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(54) GLUCOCORTICOID-SELECTIVE ANTIINFLAMMATORY AGENTS

GLOCOCORTICOID SELEKTIVE ENTZÜNDUNGSHEMMENDE MITTEL

AGENTS ANTI-INFLAMMATOIRES A SELECTIVITE GLUCOCORTICOIDE

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(73) Proprietors:
- **Abbott Laboratories**
Abbott Park, Illinois 60064-3500 (US)
- **LIGAND PHARMACEUTICALS INCORPORATED**
San Diego, California 92121 (US)

(72) Inventors:
- **COUGHLAN, Michael, J.**
Grayslake, IL 60030 (US)
- **KORT, Michael, E.**
Lake Bluff, IL 60044 (US)
- **EDWARDS, James, P.**
San Diego, CA 92129 (US)
- **JONES, Todd, K.**
Solana Beach, CA 92075 (US)

(74) Representative: **Modiano, Guido, Dr.-Ing. et al**
Modiano, Josif, Pisanty & Staub,
Baaderstrasse 3
80469 München (DE)

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52

Description

Technical Field

[0001] The present invention relates to glucocorticoid receptor-selective benzopyrano[3,4-f]quinolines that are useful for treating immune or autoimmune diseases, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation, inflamatory disease, immune, and autoimmune diseases in a mammal.

Background of The Invention

[0002] Intracellular receptors (IR's) are a class of structurally related proteins involved in the regulation of gene expression. The steroid hormone receptors are a subset of this superfamily whose natural ligands are typically comprised of endogenous steroids such as estradiol, progesterone, and cortisol. Man-made ligands to these receptors play an important role in human health and, of these receptors, the glucocorticoid receptor (GR) has an essential role in regulating human physiology and immune response. Steroids which interact with GR have been shown to be potent antiinflammatory agents. Despite this benefit, steroidal GR ligands are not selective. Side effects associated with chronic dosing are believed to be the result of cross-reactivity with other steroid receptors such as estrogen, progesterone, androgen, and mineralocorticoid receptors which have somewhat homologous ligand binding domains.

[0003] Selective GR repressors, agonists, partial agonists and antagonists of the present disclosure can be used to influence the basic, life-sustaining systems of the body, including carbohydrate, protein and lipid metabolism, and the functions of the cardiovascular, kidney, central nervous, immune, skeletal muscle, and other organ and tissue systems, In this regard, GR modulators have proven useful in the treatment of inflammation, tissue rejection, auto-immunity, various malignancies, such as leukemias and lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, modulation of the Th1/Th2 cytokine balance, chronic kidney disease, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, and Little's syndrome.

[0004] GR modulators are especially useful in disease states involving systemic inflammation such as inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, osteoarthritis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, and cirrhosis. GR active compounds have also been used as immunostimulants and repressors, and as wound healing and tissue repair agents.

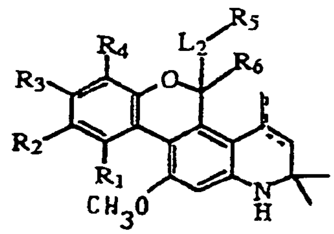
[0005] GR modulators have also found use in a variety of topical diseases such as inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type 1 reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitus, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma.

[0006] Selective antagonists of the glucocorticoid receptor have been unsuccessfully pursued for decades. These agents would potentially find application in several disease states associated with Human Immunodeficiency Virus (HIV), cell apoptosis, and cancer including, but not limited to, Kaposi's sarcoma, immune system activation and modulation, desensitization of inflammatory responses, IL-1 expression, anti-retroviral therapy, natural killer cell development, lymphocytic leukemia, and treatment of retinitis pigmentosa. Cogitive and behavioral processes are also susceptible to glucocorticoid therapy where antagonists would potentially be useful in the treatment of processes such as cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, stroke, sleep disorders, and anxiety.

[0007] WO 96/19458 discloses non-steroidal compounds which are high affinity, high selectivity modulators for steroid receptors. Pharmacological data are presented which indicate that the disclosed compounds have a high affinity to progesterone receptor with little or no cross-reactivity on glucocorticoid receptor.

Summary of The Invention

[0008] In one embodiment of the present invention are compounds represented by Formula I



I.

or pharmaceutically acceptable salts thereof, where the symbol ----- represents a single or double bond, provided that no two double bonds are in adjacent positions;

R_1, R_2, R_3, and R_4 are independently hydrogen or E; or

R_1 and R_2 together are -X*-Y*-Z*- where X* is -O- or -CH_2-, Y* is -C(O)- or -$(C(R_{12})(R_{13}))_v$ - where R_{12} and R_{13} are independently hydrogen or alkyl of one to twelve carbons and v is 1, 2, or 3, and Z* is selected from -CH_2-, -$CH_2S(O)_t$- where t is 0,1 or 2, -CH_2O-, -CH_2NR_7- where R_7 is as defined below, -NR_7- where R_7 is as defined below, and -O-;

E is -L_E-R_E where L_E is selected from

(1) a covalent bond,
(2) -O-,
(3) -$S(O)_t$-,
(4) -C(X)-, where X as used herein is selected from O or S,
(5) -NR_7- where R_7 as used herein is selected from

(a) hydrogen,
(b) aryl
(c) cycloalkyl of three to twelve carbons,
(d) alkanoyl where the alkyl part is one to twelve carbons,
(e) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(f) alkoxycarbonyl where the alkyl part is one to twelve carbons and is substituted by 1 or 2 aryl groups,
(g) alkyl of one to twelve carbons,
(h) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,
(i) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(j) alkynyl of three to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(6) -$NR_8C(X)NR_9$- where R_8 and R_9 as used herein are independently selected from

(a) hydrogen,
(b) aryl,
(c) cycloalkyl of three to twelve carbons,
(d) alkyl of one to twelve carbons,
(e) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,
(f) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(g) alkynyl of three to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(7) -X'C(X)- where X' as used herein is O or S,

(8) -C(X)X'-,
(9) -X'C(X)X"- where X" as used herein is O or S, provided that when X is O, at least one of X' or X" is O,
(10) $-NR_8C(X)-$,
(11) $-C(X)NR_8-$,
(12) $-NR_8C(X)X'-$,
(13) $-X'C(X)NR_8-$,
(14) $-SO_2NR_8-$,
(15) $-NR_8SO_2-$, and
(16) $-NR_8SO_2NR_9-$

where (6)-(16) are drawn with their right ends attached to R_E and

R_E is selected from

(1) -OH,
(2) -OG where G is a -OH protecting group,
(3) -SH,
(4) -CN,
(5) halo,
(6) haloalkoxy of one to twelve carbons,
(7) perfluoroalkoxy of one to twelve carbons,
(8) -CHO,
(9) $-NR_7R_{7'}$ where $R_{7'}$ as used herein is selected from

(a) hydrogen,
(b) aryl,
(c) cycloalkyl of three to twelve carbons,
(d) alkanoyl where the alkyl part is one to twelve carbons,
(e) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(f) alkoxycarbonyl where the alkyl part is one to twelve carbons and is substituted by 1 or 2 aryl groups,
(g) alkyl of one to twelve carbons,
(h) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,
(i) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(j) alkynyl of three to twelve carbons,
provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(10) $-C(X)NR_8R_9$,
(11) $-OSO_2R_{11}$ where R_{11} as used herein is selected from

(a) aryl,
(b) cycloalkyl of three to twelve carbons,
(c) alkyl of one to twelve carbons,
(d) alkyl of one to twelve carbons substituted with 1, 2, 3, or 4 halo substituents, and
(e) perfluoroalkyl of one to twelve carbons,

provided that when R_E is (1)-(11), L_E is a covalent bond,
(12) alkyl of one to twelve carbons,
(13) alkenyl of two to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to L_E when L_E is other than a covalent bond,
(14) alkynyl of two to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_E when L_E is other than a covalent bond,
where (12), (13), and (14) can be optionally substituted with 1, 2, or 3 substituents independently selected from

(a) alkoxy of one to twelve carbons,
(b) -OH,

provided that no two -OH groups are attached to the same carbon,

(c) -SH,

provided that no two -SH groups are attached to the same carbon,

(d) -CN,

(e) halo,

(f) -CHO,

(g) $-NO_2$,

(h) haloalkoxy of one to twelve carbons,

(i) perfluoroalkoxy of one to twelve carbons,

(j) $-NR_7R_{7'}$,

(k) $=NNR_7R_{7'}$,

(l) $-NR_7NR_{7'}R_{7''}$ where

$R_{7''}$ is selected from

(i) hydrogen,

(ii) aryl,

(iii) cycloalkyl of three to twelve carbons,

(vi) alkanoyl where the alkyl part is one to twelve carbons,

(v) alkoxycarbonyl where the alkyl part is one to twelve carbons,

(vi) alkoxycarbonyl where the alkyl part is one to twelve carbons substituted by 1 or 2 aryl groups,

(vii) alkyl of one to twelve carbons,

(viii) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,

(ix) alkenyl of three to twelve carbons,

provided that a carbon-carbon double bond is not attached directly to nitrogen, and

(x) alkynyl of three to twelve carbons,

provided that a carbon-carbon triple bond is not attached directly to nitrogen,

(m) $-CO_2R_{10}$ where R_{10} as used herein is selected from

(i) aryl,

(ii) aryl substituted with 1, 2, or 3 alkyl of one to twelve carbon substituents,

(ii) cycloalkyl of three to twelve carbons,

(iii) alkyl of one to twelve carbons, and

(iv) alkyl of one to twelve carbons substituted with aryl or cycloalkyl of three to twelve carbons,

(n) $-C(X)NR_8R_9$,

(o) $=N-OR_{10}$,

(p) $=NR_{10}$,

(q) $-S(O)_tR_{10}$,

(r) $-X'C(X)R_{10}$,

(s) (=X), and

(t) $-OSO_2R_{11}$,

(15) cycloalkyl of three to twelve carbons,

(16) cycloalkenyl of four to twelve carbons,

provided that a carbon of a carbon-carbon double bond is not attached directly to L_E when L_E is other than a covalent bond,

where (15) and (16) can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(a) alkyl of one to twelve carbons,

(b) aryl,

(c) alkoxy of one to twelve carbons,

(d) halo, and

(e) -OH,

provided that no two -OH groups are attached to the same carbon,

(17) perfluoroalkyl of one to twelve carbons,

(18) aryl, and
(19) heterocycle
where (18) and (19) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(a) alkyl of one to twelve carbons,
(b) alkanoyloxy where the alkyl part is one to twelve carbons,
(c) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(d) alkoxy of one to twelve carbons,
(e) halo,
(f) -OH,
provided that no two -OH groups are attached to the same carbon,
(g) thioalkoxy of one to twelve carbons,
(h) perfluoroalkyl of one to twelve carbons,
(i) $-NR_7R_{7'}$,
(j) $-CO_2R_{10}$,
(k) $-OSO_2R_{11}$, and
(l) (=X);

L_2 is selected from

(1) a covalent bond,
(2) alkylene of one to twelve carbons,
(3) alkylene of one to twelve carbons substituted with 1 or 2 substituents independently selected from

(a) spiroalkyl of three to eight carbon atoms,
(b) spiroalkenyl of five or eight carbon atoms,
(c) oxo,
(d) halo, and
(e) -OH,
provided that no two -OH groups are attached to the same carbon,

(4) alkynylene of two to twelve carbons,
(5) $-NR_7-$,
(6) -C(X)-,
(7) -O-, and
(8) $-S(O)_t-$; and

R_5 is selected from

(1) halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
provided that when R_5 is (1), (2), or (3), L_2 is a covalent bond,
(4) alkyl of one to twelve carbons,
(5) alkynyl two to twelve carbons,
provided that a carbon of a carbon-carbon triple bond is not attached directly to L_2 when L_2 is other than a covalent bond,
(6) cycloalkyl of three to twelve carbons,
(7) heterocycle,
(8) aryl
where (4)-(8) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(a) -OH,
provided that no two -OH groups are attached to the same carbon,
(b) -SH,
provided that no two -SH groups are attached to the same carbon,
(c) -CN,
(d) halo,

(e) -CHO,
(f) $-NO_2$,
(g) haloalkoxy of one to twelve carbons,
(h) perfluoroalkoxy of one to twelve carbons,
(i) $-NR_{8'}R_{9'}$ where $R_{8'}$ and $R_{9'}$ as used herein are independently selected from

(i) hydrogen,
(ii) alkanoyl where the alkyl part is one to twelve carbons,
(iii) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(iv) alkoxycarbonyl where the alkyl part is one to twelve carbons and is substituted with 1 or 2 phenyl substituents,
(v) cycloalkyl of three to twelve carbons,
(vi) alkyl of one to twelve carbons,
(vii) alkyl of one to twelve carbons substituted with 1, 2, or 3 substituents independently selected from
alkoxy of one to twelve carbons,
cycloalkyl of three to twelve carbons, and aryl,
(viii) alkenyl of three to twelve carbons,
provided that a carbon of a carbon-carbon double bond is not directly attached to nitrogen,
(ix) alkynyl of three to twelve carbons,
provided that a carbon of a carbon-carbon triple bond is not directly attached to nitrogen,
(x) aryl,
(xi) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to twelve carbons,
alkanoyloxy where the alkyl part is one to twelve carbons, alkoxycarbonyl where the alkyl part is one to twelve carbons, alkoxy of one to twelve carbons,
halo,
-OH
provided that no two -OH groups are attached to the same carbon,
thioalkoxy of one to twelve carbons,
perfluoroalkyl of one to twelve carbons,
$-NR_7R_{7'}$,
$-CO_2R_{10}$,
$-OSO_2R_{11}$, and
(=X), or
$R_{8'}$ and $R_{9'}$ together with the nitrogen atom to which they are attached form a ring selected from

(i) aziridine,
(ii) azetidine,
(iii) pyrrolidine,
(iv) piperidine,
(v) pyrazine,
(vi) morpholine,
(vii) thiomorpholine, and
(viii) thiomorpholine sulfone

where (i)-(viii) can be optionally substituted with 1, 2, or 3 alkyl of one to twelve carbon substituents,
(j) $=NNR_{8'}R_{9'}$,
(k) $-NR_7NR_{8'}R_{9'}$,
(l) $-CO_2R_8$,
(m) $-C(X)NR_{8'}R_{9'}$,
(n) $=N-OR_8$,
(o) $=NR_8$,
(p) $-S(O)_tR_{10}$,
(q) $-X'C(X)R_8$,
(r) (=X),
(s) $-O-(CH_2)_q-Z-R_{10}$ where R_{10} is defined previously, q as used herein is 1, 2, or 3, and Z as used herein is O or $-S(O)_t-$,
(t) $-OC(X)NR_{8'}R_{9'}$,

(u) $-OSO_2R_{11}$,
(v) alkanoyloxy where the alkyl group is one to twelve carbons,
(w) $-L_BR_{30}$ where L_B as used herein is selected from

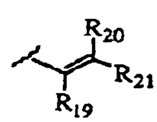
(i) a covalent bond,
(ii) -O-,
(iii) $-S(O)_t-$, and
(iv) -C(X)- and

R_{30} as used herein is selected from

(i) alkyl of one to twelve carbons,
(ii) alkenyl of one to twelve carbons,
provided that a carbon of a carbon-carbon double bond is not attached directly to L_B when L_B is other than a covalent bond,
(iii) alkynyl of one to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_B when L_B is other than a covalent bond,
where (i), (ii), and (iii) can be optionally substituted with cycloalkyl of three to twelve carbons,
-OH,
provided that no two -OH groups are attached to the same carbon,
aryl, and
heterocycle,
(iv) aryl,
(v) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to twelve carbons,
halo,
$-NO_2$, and
-OH,
provided that no two -OH groups are attached to the same carbon,
(vi) heterocycle, and
(vii) heterocycle substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to twelve carbons,
halo,
$-NO_2$, and
-OH,
provided that no two -OH groups are attached to the same carbon,

(x) $-X'C(X)X''R_{10}$,
(y) $-C(=NR_7)OR_{10}$, and
(2) $-NR_7(X)NR_{8'}R_{9'}$,

(9)



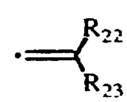
provided that when R_5 is (9), L_2 is other than $-NR_7-$ or -O-, where the carbon-carbon double bond is in the Z or E configuration, and R_{19}, R_{20}, and R_{21} are independently selected from

(a) hydrogen,
(b) halo,
(c) alkyl of one to twelve carbons, and
(d) alkyl of one to twelve carbons substituted with

(i) alkoxy of one to twelve carbons,

(ii) -OH,
provided that no two -OH groups are attached to the same carbon,
(iii) -SH,
provided that no two -SH groups are attached to the same carbon,
(iv) -CN,
(v) halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) haloalkoxy of one to twelve carbons,
(ix) perfluoroalkoxy of one to twelve carbons,
(x) $-NR_{8'}R_{9'}$
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) (=X),
(xx) $-O-(CH_2)_q-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_BR_{30}$,
(xxiii) alkanoyloxy where the alkyl group is one to twelve carbons,
(xxiv) $-OSO_2R_{11}$, and
(xxv) $-NR_7(X)NR_{8'}R_{9'}$, or
R_{20} and R_{21} together are selected from

(a) cycloalkyl of three to twelve carbon atoms,
(b) cycloalkenyl of four to twelve carbon atoms, and
(c)



(allene) where R_{22} and R_{23} are independently hydrogen or alkyl of one to twelve carbons, and

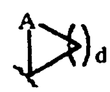
(10) cycloalkenyl of four to twelve carbons
where the cycloalkenyl group or the ring formed by R_{20} and R_{21} together can be optionally substituted with one or two substituents independently selected from

(a) alkoxy of one to twelve carbons,
(b) -OH,
provided that no two -OH groups are attached to the same carbon,
(c) -SH,
provided that no two -SH groups are attached to the same carbon,
(d) -CN,
(e) halo,
(f) -CHO,
(g) $-NO_2$,
(h) haloalkoxy of one to twelve carbons,
(i) perfluoroalkoxy of one to twelve carbons,
(j) $-NR_{8'}R_{9'}$
(k) $=NNR_{8'}R_{9'}$,
(l) $-NR_7NR_{8'}R_{9'}$,
(m) $-CO_2R_{10}$,

(n) $-C(X)NR_{8'}R_{9'}$,
(o) $=N-OR_{10}$,
(p) $=NR_{10}$,
(q) $-S(O)_tR_{10}$,
(r) $-X'C(X)R_{10}$,
(s) (=X),
(t) $-O-(CH_2)_q-Z-R_{10}$,
(u) $-OC(X)NR_{8'}R_{9'}$,
(v) $-L_BR_{30}$,
(w) alkanoyloxy where the alkyl group is one to twelve carbons,
(x) $-OSO_2R_{11}$, and
(y) $-NR_7(X)NR_{8'}R_{9'}$;

R_6 is hydrogen or alkyl of one to twelve carbon atoms; or $-L_2-R_5$ and R_6 together are

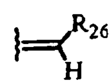
(1)



where d is 1, 2, 3, or 4 and A is selected from

(a) $-CH_2-$,
(b) $-O-$,
(c) $-S(O)_t$, and
(d) $-NR_7-$, or

(2)



where the carbon-carbon double bond can be in the E or Z configuration and R_{26} is selected from

(a) aryl,
(b) heterocycle,
(c) alkyl of one to twelve carbons,
(d) cycloalkyl of three to twelve carbons,
(e) cycloalkenyl of four to twelve carbons, and
(f) cycloalkenyl of four to twelve carbons where (a)-(f) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkoxy of one to twelve carbons,
(ii) -OH,
provided that no two -OH groups are attached to the same carbon,
(iii) -SH,
provided that no two -SH groups are attached to the same carbon,
(iv) -CN,
(v) halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) haloalkoxy of one to twelve carbons,
(ix) perfluoroalkoxy of one to twelve carbons,

(x) $-NR_{8'}R_{9'}$
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) (=X),
(xx) $-O-(CH_2)_q-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_BR_{30}$,
(xxiii) alkanoyloxy where the alkyl group is one to twelve carbons,
(xxiii) $-OSO_2R_{11}$, and
(xxiv) $-NR_7(X)NR_{8'}R_{9'}$.

[0009] Preferred embodiments of the invention are those compounds where R_1 is hydrogen or $-L_E-R_E$ where L_E is selected from

(1) a covalent bond,

(2) -O-,
(3) -C(O)O-,
(4) -OC(O)-, and
(5) -OC(O)O- and,

R_E is selected from

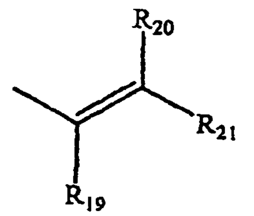
(1) alkyl of one to twelve carbons,
(2) alkenyl of two to twelve carbons,
(3) alkynyl of two to twelve carbons where (1)-(3) can be optionally substituted,
(4) -OH, and
(5) $-NR_7R_7$;

R_2 is H, or $-O-R_E$ where R_E is alkyl of one to twelve carbons;
R_3 and R_4 are hydrogen;
L_2 is selected from

(l) covalent bond,
(2) alkylene of one to twelve carbons, and
(3) $-NR_7-$;

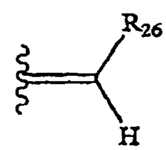
R_5 is selected from

(1) halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
(4) alkyl of one to twelve carbons,
(5) alkynyl of two to twelve carbons,
(6) heterocycle,
(7) aryl, and
(8)



where (4)-(7) and the substituents defined by R_{19}, R_{20}, and R_{21} separately or together can be optionally substituted; and

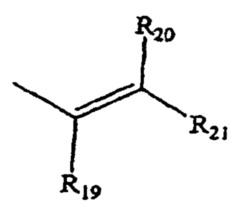
R_6 is hydrogen; or
$-L_2-R_5$ and R_6 together are



where the substituents defined by R_{26} can be optionally substituted.

[0010] More preferred are those compounds where

R_1, R_2, R_3, R_4, and R_6 are hydrogen;
L_2 is a covalent bond or alkylene of one to twelve carbons; and
R_5 is a monocyclic aromatic carbocyclic ring or of the formula



where the monocyclic aromatic carbocyclic ring is optionally substituted with one or more halogen atoms, and the substituents defined by R_{19} and R_{20} and R_{21} separately or together can be optionally substituted.

[0011] The compounds of the invention are useful for manufacturing a medicament for selectively partially antagonizing, agonizing or modulating the glucocorticoid receptor.

[0012] The compounds of the invention are useful for manufacturing a medicament for treating diseases, such as inflammation and immune, autoimmune, and inflammatory diseases in a mammal, comprising administering an effective amount of a compound having Formula I.

[0013] In yet another embodiment of the invention are disclosed pharmaceutical compositions containing compounds of Formula I.

[0014] Compounds of this invention include, but are not limited to,
2,5-dihydro-11-methoxy-5-phenyl-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline, 2,5-dihydro-11-methoxy-5-(2-propenyl)-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline,

2,5-dihydro-11-methoxy-5-(3,5-dichlorophenyl)-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline, and
2,3,5-trihydro-11-methoxy-5-(3,5-dichlorophenyl)-2,2-dimethyl-4-methylene-1H-[1]benzopyrano[3,4-f]quinoline.

Detailed Description of The Invention

Definition of Terms

[0015] The term "alkanoyl" refers to an alkyl group attached to the parent molecular group through a carbonyl group.

[0016] The term "alkanoyloxy" refers to an alkanoyl group attached to the parent molecular group through an oxygen atom.

[0017] The term "alkenyl" refers to a monovalent straight or branched chain group of two to twelve carbons derived from a hydrocarbon having at least one carbon-carbon double bond.

[0018] The term "alkoxy" refers to an alkyl group attached to the parent molecular group through an oxygen atom.

[0019] The term "alkoxycarbonyl" refers to an ester group, i.e. an alkoxy group attached to the parent molecular moiety through a carbonyl group.

[0020] The term "alkyl" refers to a monovalent straight or branched chain group of one to twelve carbons derived from a saturated hydrocarbon.

[0021] The term "alkylene" refers to a divalent straight or branched chain group of one to twelve carbons derived from an alkane.

[0022] The term "alkynyl" refers to a monovalent straight or branched chain hydrocarbon of two to twelve carbons with at least one carbon-carbon triple bond.

[0023] The term "alkynylene" refers to a divalent straight or branched chain group of two to twelve carbons derived from an alkyne.

[0024] The term "amino refers to $-NH_2$.

[0025] The term "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane, cyclohexene, cyclopentane or cyclopentene ring.

[0026] The term "carboxy" refers to $-CO_2H$.

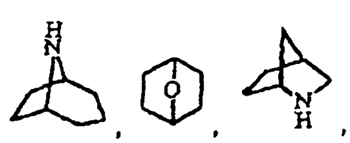
[0027] The term "cycloalkenyl" refers to a monovalent group derived from a cyclic or bicyclic hydrocarbon of three to twelve carbons that has at least one carbon-carbon double bond.

[0028] The term "cycloalkyl" refers to a monovalent group three to twelve carbons derived from a saturated cyclic or bicyclic hydrocarbon.

[0029] The term "halo" refers to F, Cl, Br, or I.

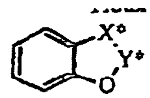
[0030] The term "heterocycle" represents a represents a 4-, 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The 4- and 5-membered rings have zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl. pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

[0031] Heterocyclics also include bridged bicyclic groups where a monocyclic heterocyclic group is bridged by an alkylene group such as



and the like.

[0032] Heterocyclics also include compounds of the formula



where X* is selected from $-CH_2-$, $-CH_2O-$ and -O-, and Y* is selected from -C(O)- and $-(C(R'')_2)_v-$, where R" is hydrogen or alkyl of one to four carbons, and v is 1-3. These heterocycles include 1,3-benzodioxolyl, 1,4-benzodioxanyl, and the like.

[0033] The term "N-protected amino" refers to groups intended to protect an amino group against undersirable reactions during synthetic procedures, Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

[0034] The term "O-protected carboxy" refers to a carboxylic acid protecting ester or amide group typically employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are performed. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (1981). Additionally, a carboxy protecting group can be used to form a prodrug of a compound of the invention whereby the carboxy protecting group can be readily cleaved in vivo, for example by enzymatic hydrolysis, to release the biologically active parent compound of the invention. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields as described in U.S. Pat. No. 3,840,556 and 3,719,667.

[0035] The term "oxo" refers to (=O).

[0036] Compounds of the invention can be converted to "pharmaceutically acceptable prodrugs" which represent those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

[0037] The term "prodrug" represents compounds which are rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

[0038] The term "pharmaceutically acceptable salt" represents those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*:1 - 19. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

[0039] Compounds of the present invention can exist as stereoisomers where asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substitiuents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and equal mixtures of enantiomers are designated (±). Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of enantiomers on chiral chromatographic columns. Geometric isomers can also exist in the compounds of the present invention. The present invention contemplates the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a ring. Sub-

stituents around a carbon-carbon double bond are designated as being in the Z or E configuration where the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond. The arrangement of substituents around a ring are designated as cis or trans where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds where the substituents are disposed on both the same and opposite sides of plane of the ring are designated cis/trans.

Methods for Radioligand Binding Studies with Human Glucocorticoid and Progesterone Receptor Cytosol

[0040] The procedure described in Anal. Biochem. 1970, 37, 244-252 was used. Briefly, cytosol preparations of human glucocorticoid receptor-α [GRX] isoform and human progesterone receptor-A [PRA] isoform were obtained from Ligand Pharmaceuticals (San Diego, CA). Both receptor cDNAs were cloned into baculovirus expression vectors and expressed in insect SF21 cells. [^{3}H]-dexamethasone (Dex, specific activity 82-86 Ci/mmole) and [^{3}H]-progesterone (Prog, specific activity 97-102 Ci/mmol) were purchased from Amersham Life Sciences (Arlington Heights, IL). Glass fiber type C multiscreen MAFC NOB plates were from Millipore (Burlington, MA). Hydroxyapatide Bio-Gel HTP gel was from Bio-Rad Laboratories (Hercules, CA). Tris(hydroxymethyl)aminomethane (Tris), ethylenediaminetetraacetic acid (EDTA), glycerol, dithiothreitol (DTT) and sodium moylybdate were obtained from Sigma Chemicals (St. Louis, MO). Microscint-20 scintillation fluid was from Packard Instrument (Meriden, CT).

[0041] Stock solutions (32 mM) of compounds were prepared in dimethylsulfoxide (DMSO), and 50X solutions of test compounds were prepared from the 32 mM solution with a 50:50 mixture of DMSO/ethanol. The 50X solution was then diluted with binding buffer that contained 10 mM Tri-HCl, 1.5 mM EDTA, 10% glycerol, 1 mM DTT, 20 mM sodium molybdate, pH 7.5 @ 4°C. 1% DMSO/ethanol was present in the binding assay.

[0042] GRX and PRA binding reactions were performed in Millipore Multiscreen plates. For GR binding assays, [^{3}H] -Dex (~35,000 dpm (~0.9 nM)), GRX cytosol (~35 μg protein), test compounds and binding buffer were mixed in a total volume of 200 μL and incubated at 4 °C overnight in a plate shaker. Specific binding was defined as the difference between binding of [^{3}H]Dex in the absence and in the presence of 1μM unlabelled Dex.

[0043] For PR binding assays, [^{3}H]Prog (~36,000 dpm (~0.8 nM)), PRA cytosol (~40 μg protein), test compounds and binding buffer were mixed in a total volume of 200 μL and incubated at 4 °C at overnight in a plate shaker. Specific binding was defined as the difference between binding of [^{3}H]Prog in the absence and in the presence of 3 μM unlabelled Prog.

[0044] After an overnight incubation, 50 μL of hydroxyapatite (25 % weight/volume) slurry were added to each well and plates were incubated for 10 min at °C in a plate shaker. Plates were suctioned with a Millipore vacuum manifold and each well was rinsed with 300 μL of ice-cold binding buffer. A 250 μL aliquot of Packard Microscint-20 was added to each well and the wells were shaken at room temperature for 20 minutes. The amount of radioactivity was determined with a Packard TopCount plate reader.

Determination of Inhibition Constant (Ki)

[0045] The concentration of test compounds that inhibited 50% of specific binding (IC_{50}) was determined from a Hill analysis of the competitive binding experiments. The Ki of test compounds was determined using the Cheng-Prusoff equation $Ki = IC_{50} / (1+[L^*]/[K_L])$ where L* is the concentration of radioligand and K_L is the dissociation constant of the radioligand determined from saturation analysis. For GRX, K_L was ~1.5 nM, and for PRA, K_L was ~4.5 nM. The inhibitory potencies of compounds of this invention and their selectivity for GR and PR receptors are shown in Table 1.

Table 1

	Ki (nM)	
Example Number	GR	PR
1	230	10000
2	640	14000
3	200	10000
4	270	8600

[0046] The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

[0047] The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray. The term "parenteral" administration refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0048] Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Conversely, reduced particle size may maintain biological activity.

[0049] These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0050] In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0051] Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

[0052] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

[0053] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0054] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0055] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[0056] The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0057] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol,

1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0058] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0059] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

[0060] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and'release the active compound.

[0061] Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

[0062] Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[0063] Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

[0064] Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

[0065] Generally dosage levels of about 1 to about 50, more preferably of about 5 to about 20 mg of active compound per kilogram of body weight per day are administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

Abbreviations

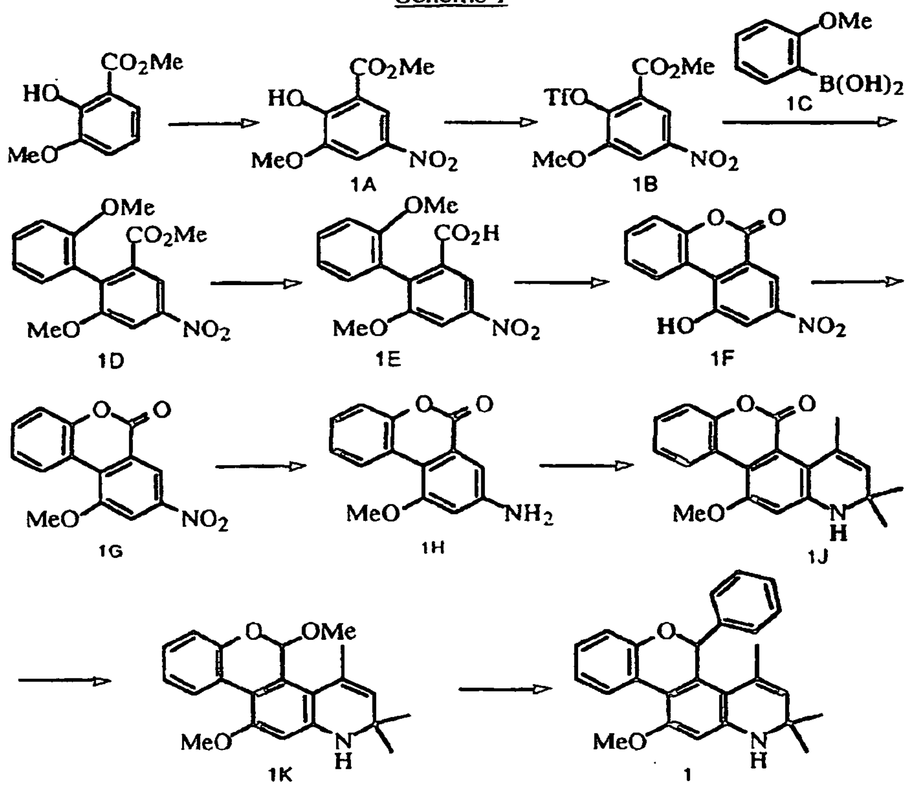
[0066] Abbreviations that have been used in the descriptions of the scheme and the examples that follow are: BF_3OEt_2 for boron trifluoride diethyl etherate; DMF for N,N-dimethylformamide, DMSO for dimethylsulfoxide; and THF for tetrahydrofuran.

Synthetic Methods

[0067] The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention can be prepared.

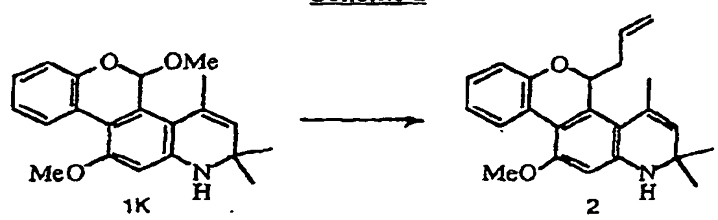
[0068] Syntheses of the compounds of the present invention are described in Schemes 1 and 2.

Scheme 1



[0069] As shown in Scheme 1, methyl 2-hydroxy-3-methoxybenzoate (isovanillin) was nitrated with sodium nitrite in the presence of an acid such as trifluoroacetic acid to provide phenol 1A. 1A was then converted to the triflate 1B with reagents such as trifluoromethanesulfonic anhydride. Lithium/halogen exchange of substrates such as 2-bromoanisole with organolithium reagents such as n-butyllithium followed by treatment of the resulting anion with a trialkyl borate such as trimethyl- or triisopropylborate and hydrolysis with strong acid such as 2M HCl provided boronic acid 1C. Condensation of 1B with 1C in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) or dichlorobis(triphenylphosphine)palladium(II) provided biphenyl 1D. Saponification 1D with a base such as lithium, sodium or potassium hydroxide provided carboxylic acid 1E. Conversion of 1E to lactone 1F was effected with Lewis acids such as BBr_3. Treatment of 1F with a non-nucleopholic base such as Cs_2CO_3 and alkylation of the resulting phenol with reagents such as dimethyl sulfate or methyl iodide produced alkyl-aryl ether 1G. Reduction of the nitro group in 1G with hydrogen gas and a palladium catalyst such as 10% palladium on carbon provided aniline 1H. Conversion of 1H to 1J was accomplished by a Skraup annulation reaction. 1J was converted to methyl acetal 1K by a two-step procedure consisting of conversion of 1J to its hemiacetal with reagents such as diisobatylaluminum hydride then acid-catalyzed etherification of the hemiacetal with acid such as p-toluenesulfonic acid monohydrate. 1J was also treated sequentially with Lewis acids such as BF_3-OEt_2 and organomagnesium chlorides, bromides, or iodides such as phenylmagnesium bromide to provide compounds exemplified by Example 1.

Scheme 2



[0070] Acetal 1K was also treated with nucleophiles such as allyltrimethylsilane in the presence of Lewis acids such as boron trifluoride diethyl etherate to form compounds exemplified by Example 2.

[0071] The compounds of the present invention and processes described herein will be better understood in connection with the following examples which are intended as an illustration of and not a limitation upon the scope of the invention as defined in the appended claims.

Example 1

2,5-dihydro-11-methoxy-5-phenyl-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline

Example 1A

[0072] A solution of methyl 2-hydroxy-3-methoxybenzoate (20.0 g, 110 mmol) in trifluoroacetic acid (150 mL) at 0 °C was treated with a solution of sodium nitrate (10.2 g, 121 mmol) in water (70 mL) over a period of 45 minutes, stirred at 0 °C for 30 minutes, and poured onto ice (450 mL). The precipitate was collected by filtration, washed with cold water, and dried under vacuum to provide the designated compound.
MS (DCI/NH_3) m/z 245 $(M+NH_4)^+$;
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.73 (s, 1H), 8.45 (d, J =7.8 Hz, 1H), 7.87 (d, J =8.2 Hz, 1H), 4.04 (s, 3H), 4.01 (s, 3H).

Example 1B

[0073] Example 1A (5.74 g, 25.3 mmol) in dichloromethane (100 mL) at -40 °C was treated with diisopropylethylamine (13.2 mL, 75.9 mmol) and freshly distilled triflic anhydride (10.0 g, 35.4 mmol) via addition funnel over a period of 30 minutes, stirred for 15 minutes at -40 °C when the starting phenol had been consumed, quenched with water (30 mL), stirred at 23 °C until a homogeneous, biphasic solution formed, and treated with dichloromethane (65 mL). The organic extract was washed with sequentially with 5% hydrochloric acid, brine, and saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. Recrystallization from hot hexanes provided the desired compound. The residue was purified by flash chromatography with 15% ethyl acetate/hexanes to provide the desired compound that can be stored indefinitely under nitrogen at -10 °C without detectable decomposition.
mp 84-86 °C
MS (DCI/NH_3) m/z 377 $(M+NH_4)^+$;
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J=7.8 Hz, 1H), 8.05 (d, J=7.7 Hz, 1H), 4.06 (s, 3H), 4.01 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 152.6, 146.6, 141.4, 126.4, 120.6, 118.1, 111.1, 57.1, 53.2;
Anal. calcd for $C_{10}H_8F_3NO_8S$: C, 33.43; H, 2.24; N, 3.89. Found: C, 33.69; H, 2.27; N, 3.81.

Example 1C

[0074] A solution of 2-bromoanisole (31.6 g, 169 mmol) in THF (320 mL) at -78 °C was treated with n-butyllithium (74.3 mL of a 2.5 M solution in hexanes, 186 mmol) for 30 minutes, stirred at -78 °C for 30 minutes, treated with triisopropylborate (48.7 mL, 211 mmol) in diethyl ether (20 mL) for 45 minutes, stirred for 30 minutes at -78 °C. stirred at 23 °C for 2 hours, poured into a mixture of ice (150 mL), 3M HCl (150 mL), and ethyl acetate (600 mL), and stirred vigorously until a homogenous biphasic solution (pH 2) formed. The layers were separated, and the organic extract was dried (Na_2SO_4), filtered, concentrated, refiltered, and washed with hexanes (2 x 30 mL) to provide the desired compound. (Note: Slow addition of triisopropylborate is essential for the avoidance of side-products resulting from overaddition of the organolithium. The boronic acid was dried under vacuum briefly (30 minutes) then stored under nitrogen until use.)

MS (DCI/NH_3) m/z 170 $(M+NH_4)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 7.67 (s, 2H), 7.57 (dd, J=7.3, 1.3 Hz, 1H), 7.87 (ddd, J=7.9, 7.4, 1.4 Hz, 1H), 6.98-6.91 (m, 2H), 3.81 (s, 3H).

Example 1D

[0075] A mechanically stirred mixture of Example 1B (7.22 g, 20.1 mmol), Example 1C (1.98 g, 13.1 mmol, 0.65 equiv), and potassium phosphate (8.53 g, 40.2 mmol) were treated sequentially with anhydrous dioxane (85 mL) and tetrakis(triphenylphosphine)palladium(0) catalyst (1.13 g, 1.00 mmol), heated at reflux for 18 hours, treated with two portions of Example 1C (1.98 g each) at 6 and 12 hour intervals, cooled to 23 °C, and partitioned between ethyl acetate (300 mL) and water (100 mL). The organic layer was washed with 10% NaOH (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography with 20% ethyl acetate/hexanes to provide the desired compound.
mp 137.5-140° C;
MS (DCI/NH_3) m/z 335 $(M+NH_4)^+$ and 318 $(M+H)^+$;
^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J=2.2 Hz, 1H), 7.93 (d, J=2.2 Hz, 1H), 7.39 (ddd, J=8.4, 7.5, 1.5 Hz, 1H), 7.12 (dd, J=7.5, 1.7 Hz, 1H), 7.04 (td, J=7.5, 1.6 Hz, 1H), 6.97 (d, J=8.5 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H);
Anal. calcd for $C_{16}H_{15}NO_6$: C, 60.56; H, 4.76; N, 4.41. Found: C, 60.64; H, 4.51; N, 4.39.

Example 1E

[0076] A solution of Example 1D (2.08 g, 6.55 mmol) in THF (10 mL) at 23 °C was treated with methanol (10 mL) and 20% KOH (10 mL), stirred at 23 °C for 6 hours, diluted with ethyl acetate (30 mL) and water (20 mL), and partitioned. The organic extract was extracted with water (10 mL) and the combined aqueous portions were cooled in ice water, acidified to pH 2 by dropwise treatment with 6M HCl, filtered, and washed in cold water (10 mL). The residue was dried under vacuum to provide the desired compound.
MS (DCI/NH_3) m/z 321 $(M+NH_4)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.12 (d, J=2.2 Hz, 1H), 7.96 (d, J=2.2 Hz, 1H), 7.33 (ddd, J=8.4, 7.6, 1.7 Hz, 1H), 7.08-7.02 (m, 2H), 6.97 (td, J=7.5, 1.2 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H).

Example IF

[0077] Example 1E (2.96 g, 9.75 mmol) in anhydrous dichloromethane (50 mL) at -78 °C was treated with boron tribromide (5.53 mL, 58.5 mmol, 6 equiv), warmed to 23 °C at which time all the boron tribromide went into solution to form a deep reddish-orange, homogenous solution, stirred at 23 °C for 12 hours, and then recooled to -78 °C, and quenched by the addition of anhydrous methanol (15 mL). The cooling bath was removed after 2 hours of stirring at -78 °C, and the reaction mixture was concentrated to remove trimethyl borate formed during the quench. The residue was treated with dichloromethane (30 mL) and methanol (3 mL), cooled to 0 °C, and filtered to provide the desired compound. The filtrate was concentrated to provide a second crop of the desired compound.
mp >270° C;
MS (DCI/NH_3) m/z 275 $(M+NH_4)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 9.0 (d, J=8.2 Hz, 1H), 8.37 (d, J=2.2 Hz, 1H), 8.04 (d, J=2.2 Hz, 1H), 7.62 (t, J=7.6 Hz, 1H), 7.46-7.38 (m, 2H).

Example 1G

[0078] A solution of Example 1F (279 mg, 1.08 mmol) and anhydrous cesium carbonate (495 mg, 1.52 mmol) in dry DMF (5 mL) at 23 °C was treated dropwise with methyl iodide (95 mL, 1.5 mmol), stirred at 23 °C for 2.5 hours, diluted with water (3 mL) and 1:1 ethyl acetate/hexane (20 mL), and stirred for 15 minutes. The solids which formed at the interface of the biphasic mixture were filtered, washed with water (3 mL), and dried under vacuum to provide the desired compound.
mp 250-253° C;
MS (DCI/NH_3) m/z 289 $(M+NH_4)^+$;
^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (dd, J=7.9, 1.4 Hz, 1H), 8.94 (d, J=2.0 Hz, 1H), 8.13 (d, J=2.1 Hz, 1H), 7.59 (ddd, J=7.9, 7.4, 1.6 Hz, 1H), 7.41 (dd, J=7.7, 1.6 Hz, 1H), 7.37 (ddd, J=7.7, 7.4, 1.4 Hz, 1H), 4.22 (s, 3H).

Example 1H

[0079] A solution of Example 1G (241 mg, 0.888 mmol) in dry dioxane (7 mL) at 23 °C was treated with 10% palladium on carbon (25 mg). A reflux condenser was attached to the reaction vessel with three-way adapter equipped with a hydrogen balloon. The solution was heated at 60° C and subjected to three purge/fill cycles with hydrogen, hydrogenated at atmospheric pressure for 24 hours, filtered through Celite® while hot, and rinsed through with additional hot THF (2 x 20 mL). The filterate was concentrated to provide the desired compound.
mp 230-235° C;
MS (DCI/NH_3) m/z 259 $(M+NH_4)^+$, 242 $(M+H)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 8.75 (dd, J=7.4, 1.9 Hz, 1H), 7.38-7.25 (m, 3H), 7.13 (d, J=2.3 Hz, 1H), 6.82 (d, J=2.3 Hz, 1H), 5.99 (br s, 2H), 3.98 (s, 3H).

Example 1J

[0080] A solution of Example 1H (202 mg, 0.837 mmol), acetone (HPLC grade, 30 mL), and iodine (70 mg, 0.276 mmol) were sealed in an ACE glass high pressure vessel (250 mL), placed in a preheated oil bath (105 °C), stirred for 10 hours at 105 °C, cooled to 23 °C, and concentrated. The resulting brown oil was purified by flash chromatography with 5%-10%-30% ethyl acetate/ hexanes) to provide the desired compound.
mp 229-231 °C;
MS (DCI/NH_3) m/z 339 $(M+NH_4)^+$, 322 $(M+H)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 8.76 (dd, J=8.1, 1.4 Hz, 1H), 7.35 (td, J=8, 0, 1.5 Hz, 1H), 7.30-7.22 (m, 2H), 6.95 (br s, 1H), 6.82 (s, 1H), 5.36 (br s, 2H), 3.97 (s, 3H), 1.90 (s, 3H), 1.22 (s, 6H);
HRMS (FAB/NBA) calcd for $C_{20}H_{20}NO_3$ $(M+H)^+$ 322.1443. Found: 322.1430;
Anal. calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.71; H,5.92; N, 4.40.

Example 1K

[0081] A solution of Example 1J (340 mg, 1.06 mmol) in anhydrous dichloromethane (10 mL) at -78 °C was treated dropwise with diisobutylaluminum hydride (2.22 mL of a 1.0 M solution in toluene, 2.22 mmol) for 20 minutes, stirred at -78 °C for 1 hour at which time TLC analysis of the reaction mixture (quenched with satd.NH_4Cl) indicated nearly complete conversion to the desired lactol and a small amount of diol resulting from over-reduction of the lactone. The solution was quenched with saturated sodium potassium tartrate (Rochelle's salt solution, 5 mL), warmed to room temperature, quenched with ethyl acetate (25 mL) and additonal saturated sodium potassium tartrate (10 mL) and stirred vigorously until a homogeneous, biphasic solution resulted. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic portions were combined, washed with brine (10 mL), and dried (Na_2SO_4), filtered and concentrated to provide the crude lactol.
[0082] The crude lactol was suspended in methanol (20 mL) at 0° C, treated with p-toluenesulfonic acid monohydrate (35 mg, 10% w/w), stirred for 1 hour, warmed to 10 °C, poured into saturated NaHC03 (20 mL), and extracted with ethyl acetate (2 x 45 mL). The extracts were washed with brine (10 mL), (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography with 30% hexanes/dichloromethane to provide the desired compound.
MS (DCI/NH_3) m/z 306 $(M-OCH_3)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 8.18 (dd, J=8.0, 1.4 Hz, 1H), 7.16-6.96 (m, 3H), 6.47 (s, 1H), 6.33 (s, 1H), 5.38 (br s, 1H), 5.08 (s, 1H), 3.81 (s, 6H), 2.18 (s, 3H), 1.27 (s, 3H), 1.06 (s, 3H).

Example 1L

2,5-dihydro-11-methoxy-5-phenyl-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline

[0083] A solution of Example 1K (94 mg, 0.278 mmol) in dichloroethane (12 mL) at -10 °C was treated with freshly distilled BF_3OEt_2 (96 mL, 0.780 mmol), stirred at -10 °C for 5 minutes, treated dropwise with phenylmagnesium bromide (279 mL of a 3.0 M solution) in diethyl ether (0.834 mmol), stirred for 30 minutes at -10 °C, poured into saturated $NaHCO_3$ (10 mL) and extracted with ethyl acetate (2 x 25 mL). The extract was washed with brine (5 mL), dried (Na_2SO_4), filtered, and cencentrated. The residue was purified by flash chromatography with toluene to provide the desired compound.
MS (DCI/NH_3) m/z 384 $(M+H)^+$;
^1H NMR (300 MHz, DMSO-d_6) δ 8.01 (dd, J=7.9, 1.3 Hz, 1H), 7.23-7.13 (m, 5H), 6.90 (td, J=7.7, 1.2 Hz, 1H), 6.83-6.72 (m, 2H), 6.78 (s, 1H), 6.48 (s, 1H), 6.34 (br s, 1H), 5.29 (s, 1H), 3.83 (s, 3H), 1.82 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H);
HRMS (FAB/NBA) calcd for $C_{26}H_{25}NO_2$ M^+: 383.1885. Found: 383.1875.

Example 2

2,5-dihydro-11-methoxy-5-(2-propenyl)-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline

[0084] A solution of Example 1K (102 mg, 0.302 mmol) and trimethylallylsilane (288 mL, 1.81 mmol) in dichloromethane (6 mL) at -78 °C was treated with freshly distilled BF_3OEt_2 (112 mL, 0.907 mmol), warmed to 23 °C, stirred for 1.5 hours, poured into saturated $NaHCO_3$ (5 mL), and extracted with ethyl acetate (2 x 20 mL). The extract was washed with brine (3 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography with 100% toluene to provide the desired compound.
mp 84-86 °C;
MS (DCI/NH_3) m/z 348 $(M+H)^+$;
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (dd, J=7.9, 1.3 Hz, 1H), 7.08 (td, J=7.8, 1.3 Hz, 1H), 6.95 (t, J=7.7 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 6.37 (s, 1H), 6.28 (s, 1H), 5.88-5.73 (m, 2H), 5.35 (s, 1H), 5.06-4.94 (m, 2H), 3.81 (s, 3H), 2.47-2.31 (m, 2H), 2.13 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H);
Anal. calcd for $C_{23}H_{25}NO$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.48; H, 7.18; N, 3.97.

Example 3

2,5-dihydro-11-methoxy-5-(3,5-dichlorophenyl)-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline

[0085] A mixture of magnesium turnings (194 mg, 8.00 mmol) and 1-bromo-3,5-dichlorobenzene, (1.81 g, 8.00 mmol) diethyl ether (10 mL) was treated with a trace of iodine and stirred at gentle reflux for 2 hours at which point all of the magnesium had been consumed. The solution of Grignard reagent was stored under nitrogen and processed immediately with Example 1K as in Example 1L to provide the desired compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04 (dd, J=7.7, 1.2 Hz, 1H), 7.52-7.43 (m, 1H), 7.13 (dd, J=7.8, 1.3 Hz, 1H), 7.00-6.78 (m, 4H), 6.80 (s, 1H), 6.52 (s, 1H), 6.47 (br s, 1H), 5.32 (br s, 1H), 3.85 (s, 3H), 1.82 (s, 3H), 1.22 (s, 3H), 1.18 (s, 3H); HRMS (FAB/NBA) calcd for $C_{26}H_{23}Cl_2NO_2$ M^+: 451.1106. Found: 451.1117.

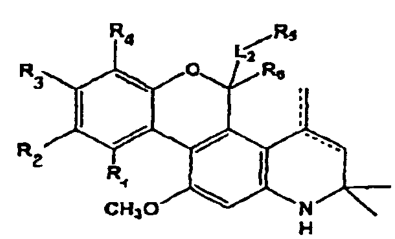
Example 4

2,3,5-trihydro-11-methoxy-5-(3,5-dichlorophenyl)-2,2 -dimethyl-4-methylene-1H-[1]benzopyrano[3,4-f]quinoline

[0086] Example 1K and 3,5-dichlorophenylmagnesium bromide were processed as in examples 1L and 3 to provide the title compound.
MS (DCI/NH_3) m/z 452 $(M+H)^+$;
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04 (dd, J=7.7, 1.2 Hz, 1H), 7.50-7.42 (m, 1H), 7.19-7.13 (m, 2H), 7.01-6.77, m, 4H), 6.70 (br s, 1H), 6.52 (s, 1H), 6.39 (s, 1H), 4.79 (br s, 1H), 1.82 (s, 3H), 2.38-2.11 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H);
HRMS (FAB/NBA) calcd for $C_{26}H_{23}Cl_2NO_2 \cdot (M^+)$: 451.1106. Found: 451.1098.

Claims

1. A compound of the Formula I



I

where the symbol ---- represents a single or double bond, provided that no two double bonds are in adjacent positions;

R_1, R_2, R_3, and R_4 are each independently hydrogen, or E; or R_1 and R_2 together are -X*-Y*-Z*- where X* is -O- or -CH_2-, Y* is -C(O)- or -(C(R_{12})(R_{13}))$_v$- where R_{12} and R_{13} are independently hydrogen or alkyl of one to twelve carbons and v is 1, 2, or 3, and Z* is selected from -CH_2-, -CH_2S(O)$_t$- where t as used herein is 0, 1, or 2,-CH_2O-, -CH_2NR_7- where R_7 is defined below, -NR_7- where R_7 is defined below, and -O-;
E is -L_E-R_E where L_E is selected from

(1) a covalent bond,
(2) -O-,
(3) -S(O)$_t$-,
(4) -C(X)-, where X as used herein is selected from O or S,
(5) -NR_7- where R_7 as used herein is selected from

(a) hydrogen,
(b) aryl,
(c) cycloalkyl of three to twelve carbons,
(d) alkanoyl where the alkyl part is one to twelve carbons,
(e) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(f) alkoxycarbonyl where the alkyl part is one to twelve carbons and is substituted by 1 or 2 aryl groups,
(g) alkyl of one to twelve carbons,
(h) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,
(i) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(j) alkynyl of three to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(6) -NR_8C(X)NR_9- where R_8 and R_9 as used herein are independently selected from

(a) hydrogen,
(b) aryl,
(c) cycloalkyl of three to twelve carbons,
(d) alkyl of one to twelve carbons,
(e) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,
(f) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(g) alkynyl of three to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(7) -X'C(X)-, where X' as used herein is selected from O or S,
(8) -C(X)X'-,
(9) -X'C(X)X"-, where X" as used herein is selected from O or S, provided that when X is O, at least one of X' or X" is O,
(10) -NR_8C(X)-,
(11) -C(X)NR_8-,
(12) -NR_8C(X)X'-,
(13) -X'C(X)NR_8-,
(14) -SO_2NR_8-,
(15) -NR_8SO_2-, and
(16) -$NR_8SO_2NR_9$-

where (6)-(16) are drawn with their right ends attached to R_E and,
R_E is selected from

(1) -OH,
(2) -OG where G is a -OH protecting group,
(3) -SH,
(4) -CN

(5) halo,
(6) haloalkoxy of one to twelve carbons,
(7) perfluoroalkoxy of one to twelve carbons,
(8) -CHO,
(9) $-NR_7R_{7'}$, where $R_{7'}$ as used herein is selected from

(a) hydrogen,
(b) aryl,
(c) cycloalkyl of three to twelve carbons,
(d) alkanoyl where the alkyl part is one to twelve carbons,
(e) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(f) alkoxycarbonyl where the alkyl part is one to twelve carbons and is substituted by 1 or 2 aryl groups,
(g) alkyl of one to twelve carbons,
(h) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected from aryl or cycloalkyl of three to twelve carbons,
(i) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(j) alkynyl of three to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,

(10) $-C(X)NR_8R_9$,
(11) $-OSO_2R_{11}$ where R_{11} as used herein is selected from

(a) aryl,
(b) cycloalkyl of three to twelve carbons,
(c) alkyl of one to twelve carbons,
(d) alkyl of one to twelve,carbons substituted with 1, 2, 3, or 4 halo substituents, and
(e) perfluoroalkyl of one to twelve carbons,
provided that when R_E is (1)-(11), L_E is a covalent bond,

(12) alkyl of one to twelve carbons,
(13) alkenyl of two to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to L_E when L_E is other than a covalent bond,
(14) alkynyl of two to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_E when L_E is other than a covalent bond, where (12), (13), and (14) can be optionally substituted with 1, 2, or 3 substituents independently selected from

(a) alkoxy of one to twelve carbons,
(b) -OH, provided that no two -OH groups are attached to the same carbon,
(c) -SH, provided that no two -SH groups are attached to the same carbon,
(d) -CN,
(e) halo,
(f) -CHO,
(g) $-NO_2$,
(h) haloalkoxy of one to twelve carbons,
(i) perfluoroalkoxy of one to twelve carbons,
(j) $-NR_7R_{7'}$,
(k) $=NNR_7R_{7'}$,
(l) $-NR_7NR_7R_{7'}$ where $R_{7'}$ is selected from

(i) hydrogen,
(ii) aryl,
(iii) cycloalkyl of three to twelve carbons,
(vi) alkanoyl where the alkyl part is one to twelve carbons,
(v) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(vi) alkoxycarbonyl where the alkyl part is one to twelve carbons substituted by 1 or 2 aryl groups,
(vii) alkyl of one to twelve carbons,
(viii) alkyl of one to twelve carbons substituted with 1 or 2 substituents independently selected

from aryl or cycloalkyl of three to twelve carbons,
(ix) alkenyl of three to twelve carbons, provided that a carbon-carbon double bond is not attached directly to nitrogen, and
(x) alkynyl of three to twelve carbons, provided that a carbon-carbon triple bond is not attached directly to nitrogen,

(m) $-CO_2R_{10}$ where R_{10} as used herein is selected from

(i) aryl,
(ii) aryl substituted with 1, 2, or 3 alkyl of one to twelve carbon substituents,
(iii) cycloalkyl of three to twelve carbons,
(iv) alkyl of one to twelve carbons, and
(v) alkyl of one to twelve carbons substituted with aryl or cycloalkyl of three to twelve carbons,

(n) $-C(X)NR_8R_9$,
(o) $=N-OR_{10}$,
(p) $=NR_{10}$,
(q) $-S(O)_tR_{10}$,
(r) $-X'C(X)R_{10}$,
(s) (=X), and
(t) $-OSO_2R_{11}$,

(15) cycloalkyl of three to twelve carbons,
(16) cycloalkenyl of four to twelve carbons,
provided that a carbon of a carbon-carbon double bond is not attached directly to L_E when L_E is other than a covalent bond, where (15) and (16) can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(a) alkyl of one to twelve carbons,
(b) aryl,
(c) alkoxy of one to twelve carbons,
(d) halo, and
(e) -OH, provided that no two -OH groups are attached to the same carbon,

(17) perfluoroalkyl of one to twelve carbons,
(18) aryl, and
(19) heterocycle
where (18) and (19) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(a) alkyl of one to twelve carbons,
(b) alkanoyloxy where the alkyl part is one to twelve carbons,
(c) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(d) alkoxy of one to twelve carbons,
(e) halo,
(f) -OH,
provided that no two -OH groups are attached to the same carbon,
(g) thioalkoxy of one to twelve carbons,
(h) perfluoroalkyl of one to twelve carbons,
(i) $-NR_7R_{7'}$,
(j) $-CO_2R_{10}$,
(k) $-OSO_2R_{11}$, and
(l) (=X);

L_2 is selected from

(1) a covalent bond,
(2) alkylene of one to twelve carbons,

(3) alkylene of two to twelve carbons substituted with 1 or 2 substituents independently selected from

(a) spiroalkyl of three to eight carbon atoms,
(b) spiroalkenyl of five or eight carbon atoms,
(c) oxo,
(d) halo, and
(e) -OH, provided that no two -OH groups are attached to the same carbon,

(4) alkynylene of two to twelve carbons,
(5) $-NR_7-$,
(6) -C(X)-,
(7) -O-, and
(8) $-S(O)_t-$; and

R_5 is selected from

(1) halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
provided that when R_5 is (1), (2), or (3), L_2 is a covalent bond,
(4) alkyl of one to twelve carbons,
(5) alkynyl two to twelve carbons,
provided that a carbon of a carbon-carbon triple bond is not attached directly to L_2 when L_2 is other than a covalent bond,
(6) cycloalkyl of three to twelve carbons,
(7) heterocycle,
(8) aryl
where (4)-(8) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(a) -OH, provided that no two -OH groups are attached to the same carbon,
(b) -SH, provided that no two -SH groups are attached to the same carbon,
(c) -CN,
(d) halo,
(e) -CHO,
(f) $-NO_2$,
(g) haloalkoxy of one to twelve carbons,
(h) perfluoroalkoxy of one to twelve carbons,
(i) $-NR_{8'}R_{9'}$, where $R_{8'}$ and $R_{9'}$ as used herein are independently selected from

(i) hydrogen,
(ii) alkanoyl where the alkyl part is one to twelve carbons,
(iii) alkoxycarbonyl where the alkyl part is one to twelve carbons,
(iv) alkoxycarbonyl where the alkyl part is one to twelve carbons and is substituted with 1 or 2 phenyl substituents,
(v) cycloalkyl of three to twelve carbons,
(vi) alkyl of one to twelve carbons,
(vii) alkyl of one to twelve carbons substituted with 1, 2, or 3 substituents independently selected from alkoxy of one to twelve carbons, cycloalkyl of three to twelve carbons, and aryl,
(viii) alkenyl of three to twelve carbons, provided that a carbon of a carbon-carbon double bond is not directly attached to nitrogen,
(ix) alkynyl of three to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not directly attached to nitrogen,
(x) aryl,
(xi) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkyl of one to twelve carbons, alkanoyloxy where the alkyl part is one to twelve carbons, alkoxycarbonyl where the alkyl part is one to twelve carbons, alkoxy of one to twelve carbons, halo, -OH provided that no two -OH groups are attached to the same carbon, thioalkoxy of one to twelve carbons, per-

fluoroalkyl of one to twelve carbons, $-NR_7R_{7'}$, $-CO_2R_{10}$, $-OSO_2R_{11}$, and (=X), or

$R_{8'}$ and $R_{9'}$ together with the nitrogen atom to which they are attached form a ring selected from

(i) aziridine,
(ii) azetidine,
(iii) pyrrolidine,
(iv) piperidine,
(v) pyrazine,
(vi) morpholine,
(vii) thiomorpholine, and
(viii) thiomorpholine sulfone
where (i)-(viii) can be optionally substituted with 1, 2, or 3 alkyl of one to twelve carbon substituents,

(j) $=NNR_{8'}R_{9'}$,
(k) $-NR_7NR_{8'}R_{9'}$,
(l) $-CO_2R_8$,
(m) $-C(X)NR_{8'}R_{9'}$,
(n) $=N-OR_8$,
(o) $=NR_8$,
(p) $-S(O)_tR_{10}$,
(q) $-X'C(X)R_8$,
(r) (=X),
(s) $-O-(CH_2)_q-Z-R_{10}$ where R_{10} is defined previously, q as used herein is 1, 2, or 3, and Z as used herein is O or $-S(O)_t-$,
(t) $-OC(X)NR_{8'}R_{9'}$,
(u) $-OSO_2R_{11}$,
(v) alkanoyloxy where the alkyl group is one to twelve carbons,
(w) $-L_BR_{30}$ where L_B as used herein is selected from

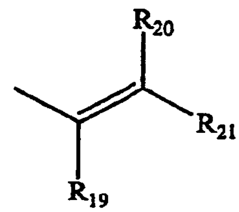
(i) a covalent bond,
(ii) -O-,
(iii) $-S(O)_t-$, and
(iv) -C(X)- and

R_{30} as used herein is selected from

(i) alkyl of one to twelve carbons,
(ii) alkenyl of two to twelve carbons, provided that a carbon of a carbon-carbon double bond is not attached directly to L_B when L_B is other than a covalent bond,
(iii) alkynyl of two to twelve carbons, provided that a carbon of a carbon-carbon triple bond is not attached directly to L_B when L_B is other than a covalent bond,
where (i), (ii), and (iii) can be optionally substituted with cycloalkyl of three to twelve carbons, -OH, provided that no two - OH groups are attached to the same carbon, aryl, and heterocycle,
(iv) aryl,
(v) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkyl of one to twelve carbons, halo, $-NO_2$, and -OH, provided that no two -OH groups are attached to the same carbon,
(vi) heterocycle, and
(vii) heterocycle substituted with 1, 2, 3, 4, or 5 substituents independently selected from alkyl of one to twelve carbons, halo, $-NO_2$, and -OH, provided that no two -OH groups are attached to the same carbon,

(x) $-X'C(X)X''R_{10}$,
(y) $-C(=NR_7)OR_{10}$, and
(z) $-NR_7(X)NR_{8'}R_{9'}$,

(9)

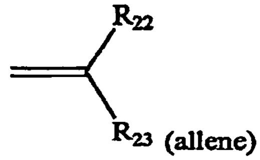


provided that when R_5 is (9), L_2 is other than $-NR_7-$ or -O-, where the carbon-carbon double bond is the Z or E configuration, and R_{19}, R_{20}, and R_{21} are independently selected from

(a) hydrogen,
(b) halo,
(c) alkyl of one to twelve carbons, and
(d) alkyl of one to twelve carbons substituted with

(i) alkoxy of one to twelve carbons,
(ii) -OH, provided that no two -OH groups are attached to the same carbon,
(iii) -SH, provided that no two -SH groups are attached to the same carbon,
(iv) -CN,
(v) halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) haloalkoxy of one to twelve carbons,
(ix) perfluoroalkoxy of one to twelve carbons,
(x) $-NR_{8'}R_{9'}$,
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) (=X),
(xx) $-O-(CH_2)_q-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_BR_{30}$,
(xxiii) alkanoyloxy where the alkyl group is one to twelve carbons,
(xxiv) $-OSO_2R_{11}$, and
(xxv) $-NR_7(X)NR_{8'}R_{9'}$, or

R_{20} and R_{21} together are selected from
(a) cycloalkyl of three to twelve carbon atoms,
(b) cycloalkenyl of four to twelve carbon atoms, and
(c)



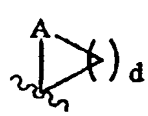
where R_{22} and R_{23} are independently hydrogen or alkyl of one to twelve carbons, and,

(10) cycloalkenyl of four to twelve carbons where the cycloalkenyl group or the ring formed by R_{20} and R_{21} together can be optionally substituted with one or two substituents independently selected from

(a) alkoxy of one to twelve carbons,
(b) -OH, provided that no two -OH groups are attached to the same carbon,
(c) -SH, provided that no two -SH groups are attached to the same carbon,
(d) -CN,
(e) halo,
(f) -CHO,
(g) $-NO_2$,
(h) haloalkoxy of one to twelve carbons,
(i) perfluoroalkoxy of one to twelve carbons,
(j) $-NR_{8'}R_{9'}$,
(k) $=NNR_{8'}R_{9'}$,
(l) $-NR_7NR_{8'}R_{9'}$,
(m) $-CO_2R_{10}$,
(n) $-C(X)NR_{8'}R_{9'}$,
(o) $=N-OR_{10}$,
(p) $=NR_{10}$,
(q) $-S(O)_tR_{10}$,
(r) $-X'C(X)R_{10}$,
(s) (=X),
(t) $-O-(CH_2)_q-Z-R_{10}$,
(u) $-OC(X)NR_{8'}R_{9'}$,
(v) $-L_BR_{30}$,
(w) alkanoyloxy where the alkyl group is one to twelve carbons,
(x) $-OSO_2R_{11}$, and
(y) $-NR_7(X)NR_{8'}R_{9'}$,

R_6 is hydrogen or alkyl of one to twelve carbon atoms; or
$-L_2-R_5$ and R_6 together are

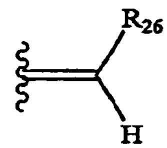
(1)



where d is 1, 2, 3, or 4 and A is selected from

(a) $-CH_2-$,
(b) -O-,
(c) $-S(O)_t$, and
(d) $-NR_7-$, or

(2)



where the carbon-carbon double bond can be in the E or Z configuration and R_{26} is selected from

(a) aryl,
(b) heterocycle,
(c) alkyl of one to twelve carbons,
(d) cycloalkyl of three to twelve carbons,
(e) cycloalkenyl of four to twelve carbons, and
(f) cycloalkenyl of four to twelve carbons where (a)-(f) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkoxy of one to twelve carbons,
(ii) -OH, provided that no two -OH groups are attached to the same carbon,
(iii) -SH, provided that no two -SH groups are attached to the same carbon,
(iv) -CN,
(v) halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) haloalkoxy of one to twelve carbons,
(ix) perfluoroalkoxy of one to twelve carbons,
(x) $-NR_{8'}R_{9'}$,
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) (=X),
(xx) $-O-(CH_2)_q-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_BR_{30}$,
(xxiii) alkanoyloxy where the alkyl group is one to twelve carbons,
(xxiv) $-OSO_2R_{11}$, and
(xxv) $-NR_7(X)NR_{8'}R_{9'}$.

or pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 where

R_1 is hydrogen or $-L_E-R_E$ where L_E is selected from

(1) a covalent bond,
(2) -O-,
(3) -C(O)O-,
(4) -OC(O)-, and
(5) -OC(O)O- and,

R_E is selected from

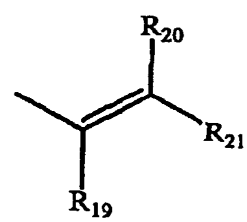
(1) alkyl of one to twelve carbons,
(2) alkenyl of two to twelve carbons,
(3) alkynyl of two to twelve carbons where (1)-(3) can be optionally substituted,
(4) -OH, and
(5) $-NR_7R_7$;

R_2 is H, or $-O-R_E$ where R_E is alkyl of one to twelve carbons;
R_3 and R_4 are hydrogen;
L_2 is selected from

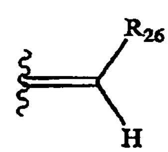
(1) covalent bond,
(2) alkylene of one to twelve carbons, and
(3) $-NR_7-$;

R_5 is selected from

(1) halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
(4) alkyl of one to twelve carbons,
(5) alkynyl of two to twelve carbons,
(6) heterocycle,
(7) aryl, and
(8)



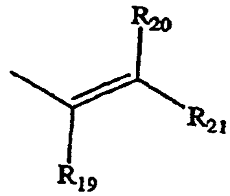
where (4)-(7) and the substituents defined by R_{19}, R_{20}, and R_{21} separately or together can be optionally substituted; and
R_6 is hydrogen; or
$-L_2-R_5$ and R_6 together are



where the substituents defined by R_{26} can be optionally substituted.

3. The compound of Claim 1 where:

R_1, R_2, R_3, R_4, and R_6 are hydrogen;
L_2 is a covalent bond or alkylene of one to twelve carbons; and
R_5 is a monocyclic aromatic carbocyclic ring or of the formula



where the monocyclic aromatic carbocyclic ring is optionally substituted with one or more halogen atoms, and the substituents defined by R_{19} and R_{20} and R_{21} separately or together can be optionally substituted.

4. The compound of any of Claims 1, 2, or 3 where the compound is selected from 2,5-dihydro-11-methoxy-5-phenyl-2,2,4-trimethyl-11H-[1]benzopyrano[3,4-f]quinoline, 2,5-dihydro-11-methoxy-5-(2-propenyl)-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline, 2,5-dihydro- 11-methoxy-5-(3,5-dichlorophenyl)-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]quinoline, and 2,3,5-trihydro-11-methoxy-5-(3,5-dichlorophenyl)-2,2-dimethyl-4-methylene-1H-[1] benzopyrano[3,4-f]quinoline.

5. A pharmaceutical composition comprising an effective amount of the compound of any of Claims 1, 2, 3, or 4, and a pharmaceutically acceptable carrier.

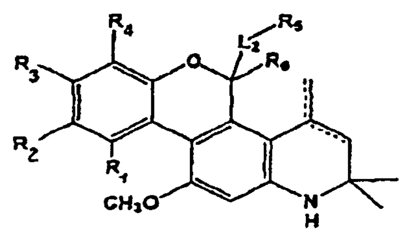
6. The use of a compound according to any of Claims 1, 2, 3, or 4, for manufacturing a medicament for selectively modulating the activation, repression, agonism, and antagonism effects of the glucocorticoid receptor in a mammal.

7. The use of a compound according to any of Claims 1, 2, 3, or 4, for manufacturing a medicament for treating inflammation and immune, autoimmune, and inflammatory diseases in a mammal.

8. A compound of any of Claims 1, 2, 3, or 4, for use as a therapeutic agent.

Patentansprüche

1. Eine Verbindung der Formel I



I

worin das Symbol —— eine Einzel- oder Doppelbindung darstellt, vorausgesetzt, daß keine zwei Doppelbindungen in angrenzenden Positionen sind;

R_1, R_2, R_3 und R_4 sind jeweils unabhängig Wasserstoff, oder E; oder R_1 und R_2 zusammen sind -X*-Y*-Z*-, worin X* -O- oder -CH_2ist, Y* ist -C(O)- oder -$(C(R_{12})(R_{13}))_v$-, worin R_{12} und R_{13} unabhängig Wasserstoff oder Alkyl von eins bis zwölf Kohlenstoffen sind, und v ist 1, 2 oder 3, und Z* ist gewählt aus -CH_2-, -$CH_2S(O)_t$-, worin t wie hierin verwendet 0, 1 oder 2 ist, -CH_2O-, -CH_2NR_7-, worin R_7 unten definiert ist, -NR_7-, worin R_7 unten definiert ist, und -O-;

E ist -L_E-R_E, worin L_E gewählt ist aus

(1) einer kovalenten Bindung,

(2) -O-,
(3) -S(O)$_t$-,
(4) -C(X)-, worin X wie hierin verwendet gewählt ist aus O oder S,
(5) -NR$_7$-, worin R$_7$ wie hierin verwendet gewählt ist aus

(a) Wasserstoff,
(b) Aryl,
(c) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(d) Alkanoyl, worin der Alkyteil von ein bis zwölf Kohlenstoffen ist,
(e) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(f) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist und substituiert ist durch 1 oder 2 Arylgruppen,
(g) Alkyl von ein bis zwölf Kohlenstoffen,
(h) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit 1 oder 2 Substituenten unabhängig gewählt aus Aryl oder Cycloalkyl von drei bis zwölf Kohlenstoffen,
(i) Alkenyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an Stickstoff gebunden ist,
(j) Alkinyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Dreifachbindung nicht direkt an Stickstoff gebunden ist,

(6) -NR$_8$C(X)NR$_9$-, worin R$_8$ und R$_9$ wie hierin verwendet unabhängig gewählt sind aus

(a) Wasserstoff,
(b) Aryl,
(c) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(d) Alkyl von ein bis zwölf Kohlenstoffen,
(e) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit 1 oder 2 Substituenten unabhängig gewählt aus Aryl oder Cycloalkyl von drei bis zwölf Kohlenstoffen,
(f) Alkenyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an Stickstoff gebunden ist,
(g) Alkinyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Dreifachbindung nicht direkt an Stickstoff gebunden ist,

(7) -X'C(X)-, worin X' wie hierin verwendet gewählt ist aus O oder S,
(8) -C(X)X'-,
(9) -X'C(X)X"-, worin X" wie hierin verwendet gewählt ist aus O oder S, vorausgesetzt daß, wenn X O ist, mindestens eins von X' oder X" O ist,
(10) -NR$_8$C(X)-,
(11) -C(X)NR$_8$-,
(12) -NR$_8$C(X)X'-,
(13) -X'C(X)NR$_8$-,
(14) -SO$_2$NR$_8$-,
(15) -NR$_8$SO$_2$-, und
(16) -NR$_8$SO$_2$NR$_9$-

worin (6)-(16) mit ihren rechten Enden an R$_E$ gebunden gezeichnet sind, und
R$_E$ ist gewählt aus

(1) -OH,
(2) -OG, worin G eine -OH Schutzgruppe ist,
(3) -SH,
(4) -CN,
(5) Halo,
(6) Haloalkoxy von ein bis zwölf Kohlenstoffen,
(7) Perfluoralkoxy von ein bis zwölf Kohlenstoffen,
(8) -CHO,
(9) -NR$_7$R$_{7'}$, worin R$_{7'}$ wie hierin verwendet gewählt ist aus

(a) Wasserstoff,
(b) Aryl,
(c) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(d) Alkanoyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(e) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(f) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist und substituiert ist durch 1 oder 2 Arylgruppen,
(g) Alkyl von ein bis zwölf Kohlenstoffen,
(h) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit 1 oder 2 Substituenten unabhängig gewählt aus Aryl oder Cycloalkyl von drei bis zwölf Kohlenstoffen,
(i) Alkenyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an Stickstoff gebunden ist,
(j) Alkinyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Dreifachbindung nicht dirket an Stickstoff gebunden ist,

(10) $-C(X)NR_8R_9$,
(11) $-OSO_2R_{11}$, worin R_{11} wie hierin verwendet gewählt ist aus

(a) Aryl,
(b) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(c) Alkyl von ein bis zwölf Kohlenstoffen,
(d) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit 1, 2, 3 oder 4 Halosubstituenten und
(e) Perfluoralkyl von ein bis zwölf Kohlenstoffen, vorausgesetzt daß, wenn R_E (1)-(11) ist, L_E eine kovalente Bindung ist,

(12) Alkyl von ein bis zwölf Kohlenstoffen,
(13) Alkenyl von zwei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff-Doppelbindung nicht direkt an L_E gebunden ist, wenn L_E anders ist als eine kovalente Bindung,
(14) Alkinyl von zwei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff-Dreifachbindung nicht direkt an L_E gebunden ist, wenn L_E anders ist als eine kovalente Bindung, worin (12), (13) und (14) wahlweise substituiert sein können mit 1, 2 oder 3 Substituenten unabhängig gewählt aus

(a) Alkoxy von ein bis zwölf Kohlenstoffen,
(b) -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(c) -SH, vorausgesetzt daß keine zwei -SH Gruppen an den gleichen Kohlenstoff gebunden sind,
(d) -CN,
(e) Halo,
(f) -CHO,
(g) $-NO_2$,
(h) Haloalkoxy von ein bis zwölf Kohlenstoffen,
(i) Perfluoralkoxy von ein bis zwölf Kohlenstoffen, (j) $-NR_7R_{7'}$,
(k) $=NNR_7R_{7'}$,
(l) $-NR_7NR_{7'}R_{7''}$, worin $R_{7''}$ gewählt ist aus

(i) Wasserstoff,
(ii) Aryl,
(iii) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(iv) Alkanoyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(v) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(vi) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist, substituiert durch 1 oder 2 Arylgruppen,
(vii) Alkyl von ein bis zwölf Kohlenstoffen,
(viii) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit 1 oder 2 Substituenten unabhängig gewählt aus Aryl oder Cycloalkyl von drei bis zwölf Kohlenstoffen,
(ix) Alkenyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß eine Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an Stickstoff gebunden ist, und
(x) Alkinyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß eine Kohlenstoff-Kohlenstoff Drei-

fachbindung nicht direkt an Stickstoff gebunden ist,

(m) -CO_2R_{10}, worin R_{10} wie hierin verwendet gewählt ist aus

(i) Aryl,
(ii) Aryl substituiert mit 1, 2 oder 3 Alkyl von ein bis zwölf Kohlenstoffsubstituenten,
(iii) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(iv) Alkyl von ein bis zwölf Kohlenstoffen, und
(v) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit Aryl oder Cycloalkyl von drei bis zwölf Kohlenstoffen,

(n) -$C(X)NR_8R_9$,
(o) =N-OR_{10},
(p) =NR_{10},
(q) -$S(O)_tR_{10}$,
(r) -$X'C(X)R_{10}$,
(s) (=X), und
(t) -OSO_2R_{11},

(15) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(16) Cycloalkenyl von vier bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff einer Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an L_E gebunden ist, wenn L_E anders ist als eine kovalente Bindung, worin (15) und (16) wahlweise substituiert sein können mit 1, 2, 3 oder 4 Substituenten unabhängig gewählt aus

(a) Alkyl von ein bis zwölf Kohlenstoffen,
(b) Aryl,
(c) Alkoxy von ein bis zwölf Kohlenstoffen,
(d) Halo, und
(e) -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,

(17) Perfluoralkyl von ein bis zwölf Kohlenstoffen,
(18) Aryl, und
(19) Heterozyklus
worin (18) und (19) wahlweise substituiert sein können mit 1, 2, 3, 4 oder 5 Substituenten unabhängig gewählt aus

(a) Alkyl von ein bis zwölf Kohlenstoffen,
(b) Alkanoyloxy, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(c) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(d) Alkoxy von ein bis zwölf Kohlenstoffen,
(e) Halo,
(f) -OH,
vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(g) Thioalkoxy von ein bis zwölf Kohlenstoffen,
(h) Perfluoralkoxy von ein bis zwölf Kohlenstoffen, (i) -$NR_7R_{7'}$,
(j) -CO_2R_{10},
(k) -OSO_2R_{11}, und
(l) (=X);

L_2 ist gewählt aus

(1) einer kovalenten Bindung,
(2) Alkylen von ein bis zwölf Kohlenstoffen,
(3) Alkylen von zwei bis zwölf Kohlenstoffen substituiert mit 1 oder 2 Substituenten unabhängig gewählt aus

(a) Spiroalkyl von drei bis acht Kohlenstoffatomen,

(b) Spiroalkenyl von fünf oder acht Kohlenstoffatomen,
(c) Oxo,
(d) Halo, und
(e) -OH,
vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,

(4) Alinylen von zwei bis zwölf Kohlenstoffen,
(5) $-NR_7-$,
(6) -C(X)-,
(7) -O-, und
(8) $-S(O)_t-$; und

R_5 ist gewählt aus

(1) Halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
vorausgesetzt daß, wenn R_5 (1), (2) oder (3) ist, L_2 eine kovalente Bindung ist,
(4) Alkyl von ein bis zwölf Kohlenstoffen,
(5) Alkinyl zwei bis zwölf Kohlenstoffen,
vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Dreifachbindung nicht direkt an L_2 gebunden ist, wenn L_2 anders ist als eine kovalente Bindung,
(6) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(7) Heterzyklus,
(8) Aryl,
worin (4)-(8) wahlweise substituiert sein können mit 1, 2, 3, 4 oder 5 Substituenten unabhängig gewählt aus

(a) -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(b) -SH, vorausgesetzt daß keine zwei -SH Gruppen an den gleichen Kohlenstoff gebunden sind,
(c) -CN,
(d) Halo,
(e) -CHO,
(f) $-NO_2$,
(g) Haloalkoxy von ein bis zwölf Kohlenstoffen,
(h) Perfluoralkoxy von ein bis zwölf Kohlenstoffen, (i) $-NR_{8'}R_{9'}$, worin $R_{8'}$ und $R_{9'}$ wie hierin verwendet unabhängig gewählt sind aus

(i) Wasserstoff,
(ii) Alkanoyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(iii) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist,
(iv) Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist und substituiert ist mit 1 oder 2 Phenylsubstituenten,
(v) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(vi) Alkyl von ein bis zwölf Kohlenstoffen,
(vii) Alkyl von ein bis zwölf Kohlenstoffen, substituiert mit 1, 2 oder 3 Substituenten unabhängig gewählt aus Alkoxy von ein bis zwölf Kohlenstoffen, Cycloalkyl von drei bis zwölf Kohlenstoffen, und Aryl,
(viii) Alkenyl von drei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an Stickstoff gebunden ist,
(ix) Alkinyl von drei bis zwölf Kohlenstoffen, vorausgesezt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff-Dreifachbindung nicht direkt an Stickstoff gebunden ist,
(x) Aryl,
(xi) Aryl substituiert mit 1, 2, 3, 4 oder 5 Substituenten unabhängig gewählt aus Alkyl von ein bis zwölf Kohlenstoffen, Alkanoyloxy, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist, Alkoxycarbonyl, worin der Alkylteil von ein bis zwölf Kohlenstoffen ist, Alkoxy von ein bis zwölf Kohlenstoffen, Halo, -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind, Thioalkoxy von ein bis zwölf Kohlenstoffen, Perfluoralkyl von ein bis zwölf Kohlen-

stoffen, $-NR_7R_{7'}$, $-CO_2R_{10}$, $-OSO_2R_{11}$, und (=X), oder

$R_{8'}$ und $R_{9'}$ zusammen mit dem Stickstoffatom, an welches sie gebunden sind, bilden einen Ring gewählt aus

(i) Aziridin,
(ii) Azetidin,
(iii) Pyrrolidin,
(iv) Piperidin,
(v) Pyrazin,
(vi) Morpholin,
(vii) Thiomorpholin, und
(viii) Thiomorpholinsulfon,
worin (i)-(viii) wahlweise substituiert sein können mit 1, 2 oder 3 Alkyl von ein bis zwölf Kohlenstoffsubstituenten,

(j) $=NNR_{8'}R_{9'}$,
(k) $-NR_7NR_{8'}R_{9'}$,
(l) $-CO_2R_8$,
(m) $-C(X)NR_{8'}R_{9'}$,
(n) $=N-OR_8$,
(o) $=NR_8$,
(p) $-S(O)_tR_{10}$,
(q) $-X'C(X)R_8$,
(r) (=X),
(s) $-O-(CH_2)_q-Z-R_{10}$, worin R_{10} vorher definiert ist, q wie hierin verwendet 1, 2 oder 3 ist und Z wie hierin verwendet 0 oder $-S(O)_t-$ ist,
(t) $-OC(X)NR_{8'}R_{9'}$,
(u) $-OSO_2R_{11}$,
(v) Alkanoyloxy, worin die Alkylgruppe von ein bis zwölf Kohlenstoffen ist,
(w) $-L_BR_{30}$, worin L_B wie hierin verwendet, gewählt ist aus

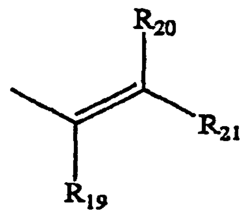
(i) einer kovalenten Bindung,
(ii) -O-,
(iii) $-S(O)_t-$, und
(iv) -C(X)- und

R_{30} wie hierin verwendet ist gewählt aus

(i) Alkyl von ein bis zwölf Kohlenstoffen,
(ii) Alkenyl von zwei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Doppelbindung nicht direkt an L_B gebunden ist, wenn L_B anders ist als eine kovalente Bindung,
(iii) Alkinyl von zwei bis zwölf Kohlenstoffen, vorausgesetzt daß ein Kohlenstoff von einer Kohlenstoff-Kohlenstoff Dreifachbindung nicht direkt an L_B gebunden ist, wenn L_B anders ist als eine kovalente Bindung,
worin (i), (ii) und (iii) wahlweise substituiert sind mit Cycloalkyl von drei bis zwölf Kohlenstoffen, -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind, Aryl und Heterozyklus,
(iv) Aryl,
(v) Aryl substituiert mit 1, 2, 3, 4 oder 5 Substituenten unabhängig gewählt aus Alkyl von ein bis zwölf Kohlenstoffen, Halo, $-NO_2$ und -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(vi) Heterozyklus, und
(vii) Heterozyklus substituiert mit 1, 2, 3, 4 oder 5 Substituenten unabhängig gewählt aus Alkyl von ein bis zwölf Kohlenstoffen, Halo, $-NO_2$ und -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,

(x) -X'C(X)X"R_{10},
(y) -C(=NR_7)OR_{10}, und
(z) -NR_7(X)NR_8'R_9',

(9)



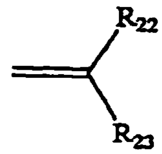
vorausgesetzt daß, wenn R_5 (9) ist, L_2 anders als -NR_7- oder -O- ist, worin die Kohlenstoff-Kohlenstoff Doppelbindung in der Z oder E Konfiguration vorliegt, und R_{19}, R_{20} und R_{21} sind unabhängig gewählt aus

(a) Wasserstoff,
(b) Halo,
(c) Alkyl von ein bis zwölf Kohlenstoffen und
(d) Alkyl von ein bis zwölf Kohlenstoffen substituiert mit

(i) Alkoxy von ein bis zwölf Kohlenstoffen,
(ii) -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(iii) -SH, vorausgesetzt daß keine zwei -SH Gruppen an den gleichen Kohlenstoff gebunden sind,
(iv) -CN,
(v) Halo,
(vi) -CHO,
(vii) -NO_2,
(viii) Haloalkoxy von ein bis zwölf Kohlenstoffen,
(ix) Perfluoralkoxy von ein bis zwölf Kohlenstoffen,
(x) -NR_8'R_9',
(xi) =NNR_8'R_9',
(xii) -NR_7NR_8'R_9',
(xiii) -CO_2R_{10},
(xiv) -C(X)NR_8'R_9',
(xv) =N-OR_{10},
(xvi) =NR_{10},
(xvii) -$S(O)_tR_{10}$,
(xviii) -X'C(X)R_{10},
(xix) (=X),
(xx) -O- $(CH_2)_q$-Z-R_{10},
(xxi) -OC(X)NR_8'R_9',
(xxii) -L_BR_{30},
(xxiii) Alkanoyloxy, worin die Alkylgruppe von ein bis zwölf Kohlenstoffen ist,
(xxiv) -OSO_2R_{11}, und
(xxv) -NR_7(X)NR_8'R_9', oder

R_{20} und R_{21} zusammen sind gewählt aus

(a) Cycloalkyl von drei bis zwölf Kohlenstoffatomen,
(b) Cycloalkenyl von vier bis zwölf Kohlenstoffatomen, und
(c)



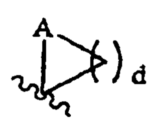
(Allen)

worin R_{22} und R_{23} unabhängig Wasserstoff sind oder Alkyl von ein bis zwölf Kohlenstoffen, und (10) Cycloalkenyl von vier bis zwölf Kohlenstoffen, worin die Cycloalkenylgruppe oder der Ring, die gebildet sinddurch R_{20} und R_{21}, zusammen wahlweise substituiert sein können mit ein oder zwei Substituenten unabhängig gewählt aus

(a) Alkoxy von ein bis zwölf Kohlenstoffen,
(b) -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(c) -SH, vorausgesetzt daß keine zwei -SH Gruppen an den gleichen Kohlenstoff gebunden sind,
(d) -CN,
(e) Halo,
(f) -CHO,
(g) $-NO_2$,
(h) Haloalkoxy von ein bis zwölf Kohlenstoffen,
(i) Perfluoralkoxy von ein bis zwölf Kohlenstoffen,
(j) $-NR_{8'}R_{9'}$,
(k) $=NNR_{8'}R_{9'}$,
(l) $-NR_7NR_{8'}R_{9'}$,
(m) $-CO_2R_{10}$,
(n) $-C(X)NR_{8'}R_{9'}$,
(o) $=N\text{-}OR_{10}$,
(p) $=NR_{10}$,
(q) $-S(O)_tR_{10}$,
(r) $-X'C(X)R_{10}$,
(s) (=X),
(t) $-O-(CH_2)_q\text{-}Z\text{-}R_{10}$,
(u) $-OC(X)NR_{8'}R_{9'}$,
(v) $-L_BR_{30}$,
(w) Alkanoyloxy, worin die Alkylgruppe von ein bis zwölf Kohlenstoffen ist,
(x) $-OSO_2R_{11}$, und
(y) $-NR_7(X)NR_{8'}R_{9'}$,

R_6 ist Wasserstoff oder Alkyl von ein bis zwölf Kohlenstoffatomen; oder
$-L_2\text{-}R_5$ und R_6 zusammen sind

(1)

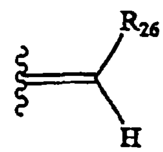


worin d 1, 2, 3 oder 4 ist und A ist gewählt aus

(a) $-CH_2-$,
(b) -O-,

(c) $-S(O)_t$, und
(d) $-NR_7-$, oder

(2)



worin die Kohlenstoff-Kohlenstoff Doppelbindung in der E oder Z Konfiguration vorliegen kann und R_{26} ist gewählt aus

(a) Aryl,
(b) Heterozyklus,
(c) Alkyl von ein bis zwölf Kohlenstoffen,
(d) Cycloalkyl von drei bis zwölf Kohlenstoffen,
(e) Cycloalkenyl von vier bis zwölf Kohlenstoffen, und
(f) Cycloalkenyl von vier bis zwölf Kohlenstoffen,
worin (a)-(f) wahlweise substituiert sein können mit 1, 2, 3, 4 oder 5 Substituenten unabhängig gewählt aus

(i) Alkoxy von ein bis zwölf Kohlenstoffen,
(ii) -OH, vorausgesetzt daß keine zwei -OH Gruppen an den gleichen Kohlenstoff gebunden sind,
(iii) -SH, vorausgesetzt daß keine zwei -SH Gruppen an den gleichen Kohlenstoff gebunden sind,
(iv) -CN,
(v) Halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) Haloalkoxy von ein bis zwölf Kohlenstoffen,
(ix) Perfluoralkoxy von ein bis zwölf Kohlenstoffen,
(x) $-NR_{8'}R_{9'}$,
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) $(=X)$,
(xx) $-O-(CH_2)-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_BR_{30}$,
(xxiii) Alkanoyloxy, worin die Alkylgruppe von eins bis zwölf Kohlenstoffen ist,
(xxiv) $-OSO_2R_{11}$, und
(xxv) $-NR_7(X)NR_{8'}R_{9'}$

oder pharmazeutisch verträgliche Salze davon.

2. Die Verbindung von Anspruch 1, worin

R_1 Wasserstoff oder $-L_E-R_E$ ist, worin L_E gewählt ist aus

(1) einer kovalenten Bindung,
(2) -O-,
(3) -C(O)O-,
(4) -OC(O)-, und
(5) -OC(O)O- und,

R_E ist gewählt aus

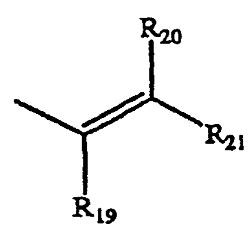
(1) Alkyl von ein bis zwölf Kohlenstoffen,
(2) Alkenyl von zwei bis zwölf Kohlenstoffen,
(3) Alinyl von zwei bis zwölf Kohlenstoffen, worin (1)-(3) wahlweise substituiert sein können,
(4) -OH, und
(5) $-NR_7R_7$;

R_2 ist H oder $-O-R_E$, worin R_E Alkyl von ein bis zwölf Kohlenstoffen ist,
R_3 und R_4 sind Wasserstoff;
L_2 ist gewählt aus

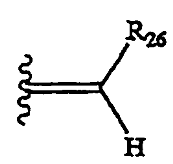
(1) einer kovalenten Bindung,
(2) Alkylen von ein bis zwölf Kohlenstoffen, und
(3) $-NR_7-$;

R_5 ist gewählt aus

(1) Halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
(4) Alkyl von ein bis zwölf Kohlenstoffen,
(5) Alkinyl von zwei bis zwölf Kohlenstoffen,
(6) Heterozyklus,
(7) Aryl, und
(8)



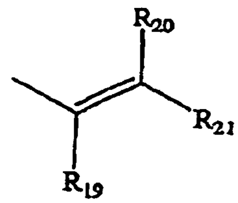
worin (4)-(7) und die Substituenten, die definiert sind durch R_{19}, R_{20} und R_{21} getrennt oder zusammen wahlweise substituiert sein können; und
R_6 ist Wasserstoff; oder
$-L_2-R_5$ und R_6 zusammen sind



worin die Substituenten definiert durch R_{26} wahlweise substituiert sein können.

3. Die Verbindung von Anspruch 1, worin:

R_1, R_2, R_3, R_4 und R_6 Wasserstoff sind;
L_2 ist eine kovalente Bindung oder Alkylen von ein bis zwölf Kohlenstoffen; und
R_5 ist ein monozyklischer aromatischer carbozyklischer Ring oder besitzt die Formel



worin der monozyklische aromatische carbozyklische Ring wahlweise substituiert ist mit einem oder mehreren Halogenatomen und die Substituenten definiert durch R_{19} und R_{20} und R_{21} getrennt oder zusammen wahlweise substituiert sein können.

4. Die Verbindung von irgendeinem der Ansprüche 1, 2 oder 3, worin die Verbindung gewählt ist aus
2,5-Dihydro-11-methoxy-5-phenyl-2,2,4-trimethyl-1H-[1]benzopyrano[3,4-f]chinolin,
2,5-Dihydro-11-methoxy-5-(2-propenyl)-2,2,4-trimethyl1H-[1]benzopyrano[3,4-f]chinolin,
2,5-Dihydro-11-methoxy-5-(3,5-dichlorphenyl)-2,2,4-trimethyl1H-[1]benzopyrano[3,4-f]chinolin, und 2,3, 5-Trihydro-11-methoxy-5-(3,5-dichlorphenyl)-2,2-dimethyl-4-methylen1H-[1]benzopyrano[3,4-f]chinolin.

5. Eine pharmazeutische Zusammensetzung, die eine wirksame Menge der Verbindung von irgendeinem der Ansprüche 1, 2, 3 oder 4 und einen pharmazeutisch verträglichen Träger umfaßt.

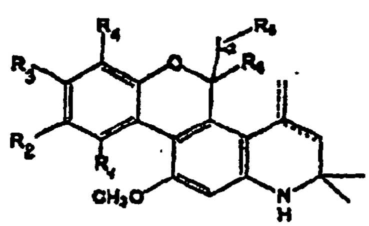
6. Die Verwendung einer Verbindung gemäß irgendeinem der Ansprüche 1, 2, 3 oder 4 zur Herstellung eines Medikaments zur selektiven Modulation von Aktivierungs-, Unterdrückungs-, Agonisierungs- und Antagonisierungseffekten des Glucocorticoidrezeptors in einem Säugetier.

7. Die Verwendung einer Verbindung gemäß irgendeinem der Ansprüche 1, 2, 3 oder 4 zur Herstellung eines Medikaments zur Behandlung von Entzündung und Immun-, Autoimmun- und entzündlichen Krankheiten in einem Säugetier.

8. Eine Verbindung von irgendeinem der Ansprüche 1, 2, 3 oder 4 zur Verwendung als ein therapeutischer Wirkstoff.

Revendications

1. Composé ayant la formule I,



I

dans laquelle le symbole ---- représente une liaison simple ou une double liaison, sous réserve que deux

doubles liaisons ne peuvent être dans des positions adjacentes ;

R_1, R_2, R_3 et R_4 sont chacun indépendamment hydrogène, ou E ; ou R_1 et R_2 sont ensemble -X*-Y*-Z*- où X* est -O- ou -CH_2-, Y* est -C(O)- ou -($C(R_{12})(R_{15})$)v- où R_{12} et R_{13} sont indépendamment hydrogène ou alkyle à un à douze atomes de carbone et v est 1, 2 ou 3, et Z* est choisi parmi -CH_2-, -$CH_2S(O)_t$ où t est ici égal à 0, 1 ou 2, -CH_2O-, -CH_2NR_7- où R_7 est défini ci-dessous, -NR_7-où R_7 est défini ci-dessous, et -O- ;
E est -L_E-R_E où L_E est choisi parmi

(1) une liaison covalente
(2) -O-,
(3) -$S(O)_t$-,
(4) -C(X)-, où X est ici choisi parmi O et S,
(5) -NR_7- où R_7 est ici choisi parmi

(a) hydrogène,
(b) aryle,
(c) cycloalkyle à trois à douze carbones,
(d) alkanoyle dont la partie alkyle est à un à douze carbones,
(e) alkyoxycarbonyle dont la partie alkyle est à un à douze carbones,
(f) alkoxycarbonyle dont la partie alkyle est à un à douze carbones et est substituée avec 1 ou 2 groupes aryle,
(g) alkyle à un à douze carbones,
(h) alkyle à un à douze atomes carbones substituée avec 1 ou 2 substituants indépendamment choisis parmi aryle ou cycloalkylke à trois à douze carbones,
(i) alkényle à trois à douze carbones, sous réserve qu'aucun carbone d'une double liaison carbone-carbone ne soit lié directement à azote
(j) alkynyle à trois à douze carbones, sous réserve qu'aucun carbone d'une triple liaison ne soit lié directement à azote,

(6) -$NR_8C(X)NR_9$- où R_8 et R_9 sont ici choisis indépendamment parmi

(a) hydrogène,
(b) aryle,
(c) cycloalkyle à trois à douze carbones,
(d) alkyle à un à douze carbones,
(e) alkyle à un à douze carbones substitué avec 1 ou 2 substituants choisis indépendamment parmi aryle ou cycloalkyle à trois à douze carbones,
(f) alkényle à trois à douze carbones, sous réserve qu'aucun carbone de double liaison carbone-carbone ne soit lié directement à azote,
(g) alkylnyle à trois à douze carbones, sous réserve qu'aucun carbone de triple liaison carbone-carbone ne soit lié directement à azote,

(7) -X'C(X)-, où X' est ici choisi parmi O et S,
(8) -C(X)X'-,
(9) -X'C(X)X"-, où X" est ici choisi parmi O et S, sous réserve que si X est 0, au moins un parmi X' et X" est O.
(10) -$NR_8C(X)$-,
(11) -$C(X)NR_8$-,
(12) -$NR_8C(X)X'$-,
(13) -$X'C(X)NR_8$-,
(14) -SO_2NR_8-,
(15) -NR_8SO_2-, et
(16) -$NR_8SO_2NR_9$-

où (6) à (16) sont inscrits de manière à ce que leurs extrémités de droite soient liées à R_8 et où R_8 est choisi parmi

(1) -OH,
(2) -OG où G est un groupe protecteur de -OH,

(3) -SH,
(4) -CN,
(5) halo,
(6) haloalkoxy à un à douze carbones,
(7) perfluoroalkoxy à un à douze carbones,
(8) -CHO,
(9) -$NR_7R_{7'}$, où $R_{7'}$ est ici choisi parmi

(a) hydrogène,
(b) aryle,
(c) cycloalkyle à trois à douze carbones,
(d) alkanoyle dont la partie alkyle est à un à douze carbones,
(e) alkoxycarbonyle dont la partie alkyle est à un à douze carbones,
(f) alkoxycarbonyle dont la partie alkyle est à un à douze carbones et substituée avec 1 ou 2 groupes aryle,
(g) alkyle à un à douze carbones,
(h) alkyle à un à douze carbones substitué avec 1 ou 2 substituants indépendamment choisis parmi aryle ou cycloalkyle à trois à douze carbones,
(i) alkényle à trois à douze carbones, sous réserve qu'aucun carbone d'une double liaison carbone-carbone ne soit lié directement à azote,
(j) alkynyle à trois à douze carbones, sous réserve qu'aucun carbone d'une triple liaison carbone-carbone ne soit lié directement à azote,

(10) -$C(X)NR_8R_9$,
(11) -OSO_2R_{11}, où R_{11} est ici choisi parmi

(a) aryle,
(b) cycloalkyle à trois à douze carbones,
(c) alkyle à un à douze carbones,
(d) alkyle à un à douze carbones substitué avec 1, 2, 3 ou 4 substituants halogène, et
(e) perfluoalkyle à un à douze carbones, sous réserve que quand R_8 est (1) à (11), L_E soit une liaison covalente,

(12) alkyle à un à douze carbones,
(13) alkényle de deux à douze carbones, sous réserve qu'aucun carbone d'une double liaison carbone-carbone ne soit directement lié à L_E quand L_E est autre qu'une liaison covalente,
(14) alkynyle de deux à douze carbones, sous réserve qu'aucun carbone d'une triple liaison carbone-carbone ne soit directement lié à L_E lorsque L_E est autre qu'une liaison covalente, où (12), (13) et (14) peuvent être facultativement substitués avec 1, 2 ou 3 substituants choisis indépendamment parmi

(a) alkoxy à un à douze carbones,
(b) -OH, sous réserve qu'il n'y ait pas deux groupes -OH liés au même carbone,
(c) -SH, sous réserve qu'il n'y ait pas deux groupes -SH liés au même carbone,
(d) -CN,
(e) halo,
(f) -CHO,
(g) -NO_2,
(h) haloalkoxy à un à douze carbones,
(i) perfluoroalkoxy à un à douze carbones,
(j) -$NR_7R_{7'}$,
(k) =$NNR_7R_{7'}$,
(k) -$NR_7NR_{7'}R_{7''}$, où $R_{7''}$ est choisi parmi

(i) hydrogène,
(ii) aryle,
(iii) cycloalkyle à trois à douze carbones
(iv) alkanoyle dont la partie alyle est à un à douze carbones,
(v) alkoxycarbonyle dont la partie alkyle est à un à douze carbones,

(vi) alkoxycarbonyle dont la partie alkyle est à un à douze carbones et substituée avec 1 ou 2 groupes aryle,
(vii) alkyle à un à douze carbones,
(viii) alkyle à un à douze carbones substitué avec 1 ou 2 substituants choisis indépendamment parmi aryle et cycloalyle à trois à douze carbones,
(ix) alkényle à trois à douze carbones, sous réserve qu'aucune double liaison carbone-carbone ne soit liée directement à azote, et
(x) alkynyle à trois à douze carbones, sous réserve qu'aucune triple liaison carbone-carbone ne soit liée directement à azote,

(m) $-CO_2R_{10}$ où R_{10} est ici choisi parmi

(i) aryle,
(ii) aryle substitué avec 1, 2, ou 3 substituants alkyle à un a douze carbones,
(iii) cycloalkyle à trois à douze carbones,
(iv) alkyle à un à douze carbones, et
(v) alkyle à un à douze carbones substitué avec aryle ou cycloalkyle à trois à douze carbones,

(n) $-C(X)NR_8R_9$,
(o) $=N-OR_{10}$,
(p) $=NR_{10}$,
(q) $-S(O)_tR_{10}$,
(r) $-X'C(X)R_{10}$,
(s) (=X), et
(t) $-OSO_2R_{11}$,

(15) cycloalkyle à trois à douze carbones,
(16) cycloalkényle à quatre à douze carbones, sous réserve qu'aucun carbone d'une double liaison carbone-carbone ne soit lié directement à L_E si L_E est autre qu'une liaison covalente, où (15) et (16) peuvent être facultativement substitués avec 1, 2, 3 ou 4 substituants choisis indépendamment parmi

(a) alkyle à un à douze carbones,
(b) aryle,
(c) alkoxy à un à douze carbones,
(d) halo, et
(e) -OH,

sous réserve qu'il n'y ait pas deux groupes -OH liés au même carbone,
(17) perfluoroalkyle a un à douze carbones,
(18) aryle, et
(19) hétérocycle
où (18) et (19) peuvent être facultativement substitués avec 1,2,3,4 ou 5 substituants choisis indépendamment parmi

(a) alkyle à un à douze carbones,
(b) alkanyloxy dont la partie alkyle est à un à douze carbones,
(c) alkoxycarbonyle dont la partie alkyle est à un à douze carbones,
(d) alkyoxy à un à douze carbones,
(e) halo,
(f) -OH,
sous réserve qu'il n'ait pas deux groupes -OH liés au même carbone,
(g) thioalkoxy à un à douze carbones,
(h) perfluoroalkyle à un à douze carbones,
(i) $-NR_7R_{7'}$,
(j) $-CO_2R_{10}$,
(k) $-OSO_2R_{11}$, et
(l) (=X) ;

L_2 est choisi parmi

(1) une liaison covalente,
(2) alkylène à un à douze carbones,
(3) alkylène de deux à douze carbones substitué avec 1 ou 2 substituants choisis indépendamment parmi

(a) spiroalkyle à trois à huit atomes de carbone,
(b) spiroalkényle à cinq à huit atomes de carbones,
(c) oxo,
(d) halo, et
(e) -OH,

sous réserve qu'il n'y ait pas deux groupes-OH liés au même carbone,
(4) alkynylène à deux à douze carbones,
(5) $-NR_7-$,
(6) -C(X)-,
(7) -O-, et
(8) $-S(O)_t-$; et

R_5 est choisi parmi

(1) halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
sous réserve que quand R_5 est (1), (2) ou (3), L_2 soit une liaison covalente,
(4) alkyle à un à douze carbones,
(5) alkylnyle à un à douze carbones,
sous réserve qu'aucune triple liaison carbone-carbone ne soit liée directement à L_2 lorsque L_2 est autre qu'une liaison covalente,
(6) cycloalkyle à trois à douze carbones,
(7) hétérocycle,
(8) aryle
où (4) à (8) peuvent être facultativement substitués avec 1, 2, 3, 4 ou 5 substituants choisis indépendamment parmi

(a) -OH, sous réserve qu'il n'y ait pas deux groupes -OH liés au même carbone,
(b) -SH, sous réserve qu'il n'y ait pas deux groupes -SH liés au même carbone,
(c) -CN,
(d) halo,
(e) -CHO,
(f) $-NO_2$,
(g) haloalkoxy à un à douze carbones,
(h) perfluoroalkyoxy à un à douze carbones,

(i) $-NR_{8'}R_{9'}$, où $R_{8'}$ et $R_{9'}$ sont ici choisis indépendamment parmi
(i) hydrogène,
(ii) alkanoyle dont la partie alkyle est à un à douze carbones,
(iii) alkoxycarbonyle dont la partie alkyle est à un à douze carbones,
(iv) alkoxycarbonyle dont la partie alkyle est à un à douze carbones et est substituée avec 1 ou 2 substituants phényle,
(v) cycloalkyle à trois à douze carbones,
(vi) alkyle à un à douze carbones,
(vii) alkyle à un à douze carbones substitué avec 1, 2 ou 3 substituants choisis indépendamment parmi alkoxy à un à douze carbones, cycloalkyle à trois à douze carbones, et aryle,
(viii) alkényle à trois à douze carbones, sous réserve qu'aucun carbone d'une double liaison carbone-carbone ne soit lié directement à azote,
(ix) alkynyle à trois à douze carbones, sous réserve qu'aucun carbone d'une triple liaison carbone-carbone ne soit lié directement à azote,

(x) aryle,
(xi) aryle substitué avec 1, 2, 3, 4 ou 5 substituants choisis indépendamment parmi alkyle à un à douze carbones, alkanolyloxy dont la partie alkyle est à un à douze carbones, alkoxycarbonyle dont la partie alkle est à un à douze carbones, alkoxy à un à douze carbones, halo, -OH sous réserve qu'il n'y ait pas deux groupes -OH liés au même carbone, thioalkoxy à un à douze carbones, perfluoroalkyle à un à douze carbones, $NR_7R_{7'}$, $-CO_2R_{10}$, $-OCO_2R_{11}$, et (=X), ou
$R_{8'}$ et $R_{9'}$ ensemble avec l'atome d'azote auquel ils sont liés forment un noyau choisi parmi

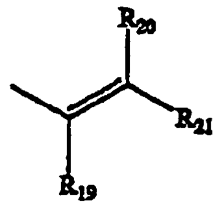
(i) aziridine,
(ii) azétidine,
(iii) pyrrolidine,
(iv) pipéridine,
(v) pyrazine,
(vi) morpholine,
(vii) thiomorpholine, et
(viii) thiomorpholine sulfone

où (i) à (viii) peuvent être facultativement substitués avec 1,2 ou 3 substituants alkyle à un à douze carbones,
(j) $=NNR_{8'}R_{9'}$,
(k) $-NR_7NR_{8'}R_{9'}$,
(l) $-CO_2R_8$,
(m) $-C(X)NR_{8'}R_{9'}$,
(n) $=N-OR_8$,
(o) $=NR_8$
(p) $-S(O)_tR_{10}$,
(q) $-X'C(X)R_8$,
(r) (=X)
(s) $-O-(CH_2)_q-Z-R_{10}$, où R_{10} est tel que défini plus haut, q est ici égal à 1, 2 ou 3 et Z est ici O ou $-S(O)_t-$,
(t) $-OC(X)NR_{8'}R_{9'}$,
(u) $-OSO_2R_{11}$,
(v) alkanoyloxy dont le groupe alkyle est à un à douze carbones,
(w) $-L_ER_{30}$ où L_E est ici choisi parmi

(i) une liaison covalente,
(ii) -O-,
(iii) $-S(O)_t$, et
(iv) -C(X)- et
R_{10} est ici choisi parmi

(i) alkyle à un à douze carbones,
(ii) alkényle à deux à douze carbones, sous réserve qu'aucun carbone d'une double liaison carbone-carbone ne soit lié directement à L_E lorsque L_E est autre qu'une liaison covalente,
(iii) alkynyle à deux à douze carbones, sous réserve qu'aucun carbone d'une triple liaison carbone-carbone ne soit lié directement à L_E lorsque L_E est autre qu'une liaison covalente,
où (i), (ii) et (iii) peuvent être facultativement substitués avec cycloalkyle à trois à douze carbones, OH, sous réserve qu'il n'y ait pas deux groupes -OH qui soient liés au même carbone, aryle, et hétérocycle,
(iv) aryle,
(v) aryle substitué avec 1, 2, 3, 4 ou 5 substituants choisis indépendamment parmi alkyle à un à douze carbones, halo, $-NO_2$, et -OH sous réserve qu'il n'y ait pas deux groupes -OH qui soient liés au même carbone,
(x) $-X'C(X)X''R_{10}$,
(y) $-C(=NR_7)OR_{10}$, et
(z) $-NR_7(X)NR_{8'}R_{9'}$,

(9)

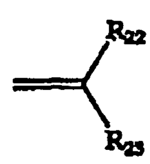


sous réserve que quand R_5 est (9), L_2 soit autre que $-NR_7-$ ou -O-, lorsque la double liaison carbone-carbone est dans la configuration Z ou E, et R_{19}, R_{20} et R_{21} sont choisis indépendamment parmi

(a) hydrogène,
(b) halo,
(c) alkyle à un à douze carbones, et
(d) alkyle à un à douze carbones substitué avec

(i) alkoxy à un à douze carbones,
(ii) -OH, sous réserve qu'il n'y ait pas deux groupes -OH qui soient liés au même carbone,
(iii) -SH, sous réserve qu'il n'y ait pas deux groupes -SH qui soient liés au même carbone,
(iv) -CN,
(v) halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) haloalkoxy à un à douze carbones,
(ix) perfluoroalkoxy à un à douze carbones,
(x) $-NR_{8'}R_{9'}$,
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) (=X),
(xx) $-O-(CH_2)_q-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_ER_{30}$,
(xxiii) alkanoyloxy dont le groupe alkyle est à un à douze carbones,
(xxiv) $-OSO_2R_{11}$, et
(xxv) $-NR_7(X)NR_{8'}R_{9'}$, ou
R_{20} et R_{21} sont choisis ensemble parmi

(a) cycloalkyle à trois à douze carbones,
(b) cycloalkényle à quatre à douze carbones, et



(allene)

(c)

où R_{22} et R_{23} sont indépendamment hydrogène ou alkyle à un à douze carbones, et

(10) cycloalkényle à quatre à douze carbones où le groupe cycloalkényle ou le noyau formé par R_{20} et R_{21} ensemble peut être facultativement substitué avec un ou plusieurs substituants choisis indépendamment parmi

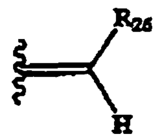
(a) alkoxy à un à douze carbones,
(b) -OH, sous réserve qu'il n'y ait pas deux groupes -OH qui soient liés au même carbone,
(c) -SH, sous réserve qu'il n'y ait pas deus groupes -SH qui soient liés au même carbone,
(d) -CN,
(e) halo,
(f) -CHO,
(g) $-NO_2$,
(h) haloalkoxy à un à douze carbones,
(i) perfluoralkoxy à un à douze carbones,
(j) $-NR_{8'}R_{9'}$,
(k) $=NNR_{8'}R_{9'}$,
(l) $-NR_7NR_{8'}R_{9'}$,
(m) $-CO_2R_{10}$,
(n) $-C(X)NR_{8'}R_{9'}$,
(o) $=N-OR_{10}$,
(p) $=NR_{10}$,
(q) $-S(O)_tR_{10}$,
(r) $-X'C(X)R_{10}$,
(s) (=X),
(t) $-O-(CH_2)_q-Z-R_{10}$,
(u) $-OC(X)NR_{8'}R_{9'}$,
(v) $-L_ER_{30}$,
(w) alkanoyloxy dont le groupe alkyle est à un à douze carbones,
(x) $-OCO_2R_{11}$, et
(y) $-NR_7(X)NR_{8'}R_{9'}$,

R_6 est hydrogène ou alkyle à un à douze atomes de carbone ; ou
$-L_2-R_5$ et R_6 ensemble sont

(1)

où d est 1, 2, 3 ou 4 et A est choisi parmi

(a) $-CH_2-$
(b) -O-
(c) $-S(O)_t$, et
(d) $-NR_7-$, ou



(2)
où la double liaison carbone-carbone peut être dans la configuration E ou Z et R_{26} est choisi parmi

(a) aryle,
(b) hétérocycle,
(c) alkyle à un à douze carbones,
(d) cycloalkyle à trois à douze carbones,
(e) cycloalkényle à quatre à douze carbones,
(f) cycloalkényle à quatre à douze carbones où (a) à (f) peuvent être facultativement substitués avec 1, 2, 3, 4 ou 5 substituants choisis indépendamment parmi

(i) alkoxy à un à douze carbones,
(ii) -OH, sous réserve qu'il n'y ait pas deux groupes -OH qui soient liés au même carbone,
(iii) -SH, sous réserve qu'il n'y ait pas deux groupes -SH qui soient liés au même carbone,
(iv) -CN,
(v) halo,
(vi) -CHO,
(vii) $-NO_2$,
(viii) haloalkoxy à un à douze carbones,
(ix) perfluoroalkoxy à un à douze carbones,
(x) $-NR_{8'}R_{9'}$,
(xi) $=NNR_{8'}R_{9'}$,
(xii) $-NR_7NR_{8'}R_{9'}$,
(xiii) $-CO_2R_{10}$,
(xiv) $-C(X)NR_{8'}R_{9'}$,
(xv) $=N-OR_{10}$,
(xvi) $=NR_{10}$,
(xvii) $-S(O)_tR_{10}$,
(xviii) $-X'C(X)R_{10}$,
(xix) (=X),
(xx) $-O-(CH_2)_q-Z-R_{10}$,
(xxi) $-OC(X)NR_{8'}R_{9'}$,
(xxii) $-L_ER_{30}$,
(xxiii) alkanoyloxy dont le groupe alkyle est à un à douze carbones,
(xxiv) $-OSO_2R_{11}$, et
(xxv) $-NR_7(X)NR_{8'}R_{9'}$,

ou des sels acceptables en pharmacie de ceux-ci.

2. Composé selon la revendication 1, dans lequel

R_1 est hydrogène ou $-L_E-R_E$ où L_E est choisi parmi

(1) une liaison covalente,
(2) -O-,
(3) -C(O)O-,
(4) -OC(O)-, et
(5) -OC(O)O et,

R_E est choisi parmi

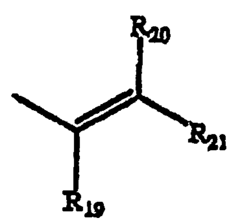
(1) alkyle d'un à douze carbones,
(2) alkényle de deux à douze carbones,
(3) alkynyle de deux à douze carbones où (1) à (3) peuvent être facultativement substitués,
(4) -OH et
(5) $-NR_7R_7$;

R_2 est H, ou $O-R_E$ ou R_E est alkyle à un à douze carbones ;
R_3 et R_4 sont hydrogène ;
L_2 est choisi parmi

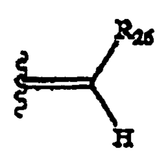
(1) liaison covalente,
(2) alkylène à un à douze carbones, et
(3) $-NR_7-$;

R_5 est choisi parmi

(1) halo,
(2) $-C(=NR_7)OR_{10}$,
(3) -CN,
(4) alkyle à un à douze carbones,
(5) alkynyle à un à douze carbones,
(6) hétérocycle,
(7) aryle, et
(8)



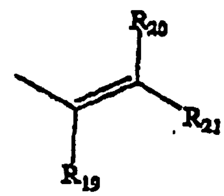
où (4) à (7) et les substituants définis par R_{19}, R_{20} et R_{21} séparément ou ensemble peuvent être facultativement substitués ; et
R_6 est hydrogène ; ou
$-L_2-R_5$ et R_6 ensemble sont



où les substituants définis par R_{26} peuvent être facultativement substitués.

3. Composé selon la revendication 1 où :

R_1, R_2, R_3, R_4 et R_6 sont hydrogène ;
L_2 est une liaison covalente ou alkylène à un à douze carbones ; et
R_5 est un noyau carbocyclique aromatique monocylique de formule



où le noyau carbocyclique aromatique monocyclique est facultativement substitué avec un ou plusieurs atomes de halogène, et les substituants définis par R_{19} et R_{20} et R_{21} séparément ou ensemble peuvent être facultativement substitués.

4. Composé selon l'une quelconque des revendications 1, 2 ou 3 où le composé est choisi parmi 2,5-dihydro-11-méthoxy-5-phényl-2,2,4-triméthyl-1H-[1]benzopyrano[3,4]quinoline, 2,5-dihydro-11-méthoxy-5-(2-propényl)-2,2,4-triméthyl-1H-[1]benzopyrano[3,4-f]quinolline, 2,5-dihydro-11-méthoxy-5-(3,5-dichlorophényl)-2,2,4-triméthyl-1H-[1]benzopyrano[3,4-f]quinoline, et 2,3,5-trihydro-11-méthoxy-5(3,5-dichlorophényl)-2,2-diméthyl-4-méthylène-1H-[1]benzopyrano[3,4-f]quinoline.

5. Composition pharmaceutique contenant une quantité efficace d'un composé selon l'une quelconque des revendications 1, 2, 3 ou 4, et un véhicule acceptable en pharmacie.

6. Usage d'un composé selon l'une quelconque des revendications 1, 2, 3 ou 4 pour la fabrication d'un médicament en vue de la modulation sélective des effets d'activation, de répression, d'agonisme et d'antagonisme du récepteur de glucocorticoïde chez un mammifère.

7. Usage d'un composé selon l'une quelconque des revendications 1, 2, 3 ou 4 pour la fabrication d'un médicament en vue du traitement de maladies immunes, auto-immunes et inflammatoires chez un mammifère.

8. Composé selon l'une quelconque des revendications 1, 2, 3 ou 4 en vue d'un usage comme agent thérapeutique.